Volume 7 **Neurology** *Number 2*

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1. Livingston, S., and Petersen, D.: New England J. Med. *254*:327 (Feb. 16) 1956.
2. Pence, L. M.: Texas State J. Med. *50*:290 (May) 1954.
3. Berman, B. A.: Am. J. Psychiat. *112*:541 (Jan.) 1956.

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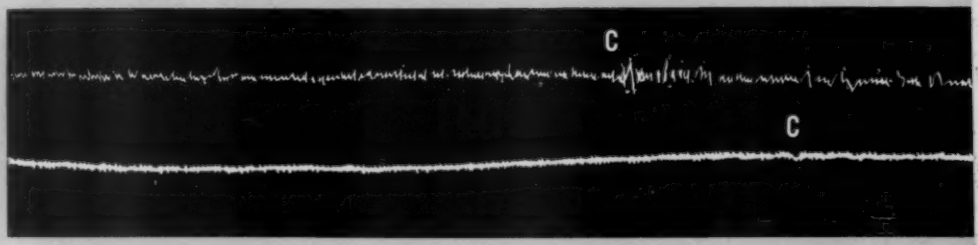

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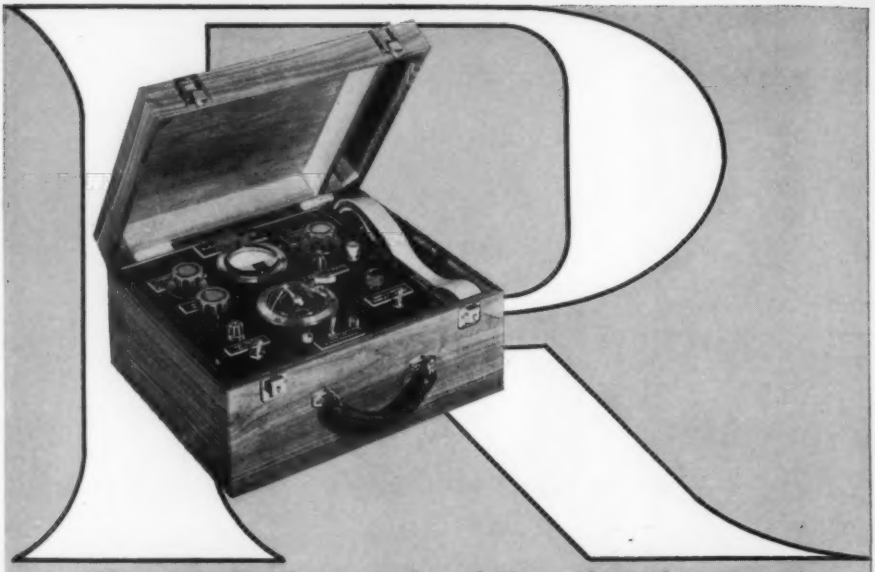

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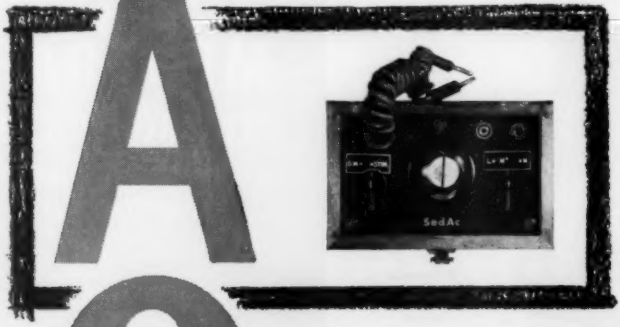

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Volume 7 Neurology Number 2

Neurologic Guides to Prognosis in Asphyxia and Anoxia

*I. M. Tarlov, M.D. and Donald Brace, M.D.**

THE ULTIMATE PURPOSE of our studies in asphyxia is to establish prognostic criteria in the sudden catastrophes which result from respiratory arrest or obstruction occurring during or immediately after various operations. The present paper is a progress report on our observations and conclusions to date. We already have an hypothesis based on observed facts and are now engaged in the next necessary step—that of testing the validity of the hypothesis by checking it against further observations.

Since more energetic attempts at resuscitation are now being made in cases of cardiac standstill and respiratory arrest, one may expect an increase in the number of survivors. Neurologists and other physicians will be called upon increasingly to pass judgment upon the likely future course of such patients.

Past attempts have been made on the basis of experimental and clinical observations in ischemia, asphyxia, and anoxia to establish a time chart showing the relation of the duration of circulatory or respiratory arrest to the likelihood of recovery. But there are many discrepancies between the neurologic changes and recovery on the one hand and the duration and severity of the anoxic insult on the other.

Fox,[1] for example, reported the case of a seven year old boy who recovered completely from cardiac arrest of 27 minutes due to proved ventricular fibrillation after treatment by cardiac massage, intravenous procaine, and adequate administration of oxygen. McFarland[2] states: "Cortical tissue does not recover if it is deprived of oxygen for more than five to ten minutes."

From the departments of neurology and neurosurgery and of anesthesiology, New York Medical College, Flower and Fifth Avenue Hospitals, New York City.
*Died January 24, 1955.

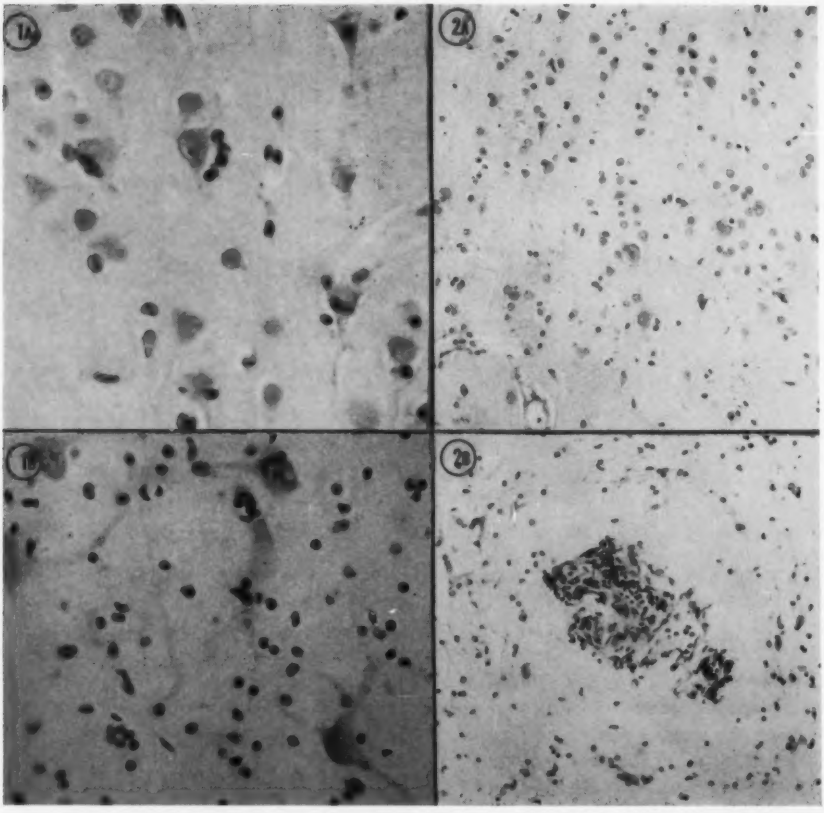

FIG. 1. Photographs taken from case 1 showing *A*, degeneration of cells of red nucleus, and *B*, perivascular round cell infiltration in red nucleus. Toluidine blue stains on tissue fixed in alcohol and embedded in celloidin.

FIG. 2. Photomicrographs taken from case 1 showing marked degeneration of cells in frontal cortex. Toluidine blue stains on tissue fixed in alcohol and embedded in celloidin.

In clinical practice it is difficult to establish such a time chart, because a variable trickle of blood or respiratory exchange, though not apparent, may often be present and affect one's correlations. We have tried, therefore, to use neurologic criteria to guide us in foretelling the patient's future course.

We wish to present briefly certain illustrative cases of asphyxia of varying degrees and to state our conclusions based on total clinical and pathologic experiences with such cases. Detailed reference to the voluminous literature on this subject will be omitted.

Even though more case material would be desirable to fully validate our conclusions, they are presented in the hope of stimulating observations and thoughts on this important problem, and of focus-

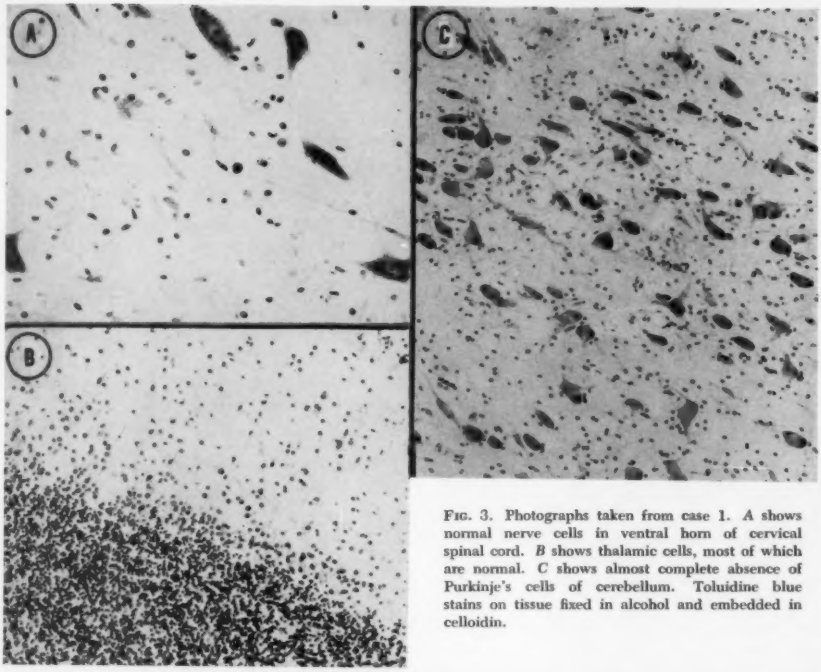

FIG. 3. Photographs taken from case 1. *A* shows normal nerve cells in ventral horn of cervical spinal cord. *B* shows thalamic cells, most of which are normal. *C* shows almost complete absence of Purkinje's cells of cerebellum. Toluidine blue stains on tissue fixed in alcohol and embedded in celloidin.

ing attention on its seriousness and on the need for means of avoiding this catastrophe. The cases are arranged in order of decreasing severity. Only the details relevant to the anoxic effects on the central nervous system are included.

GROUP 1

Case 1. An 18 year old man was hospitalized on December 23, 1945 with the diagnosis of acute appendicitis. He was taken to the operating room immediately, and preoperative medication consisted of Nembutal 1½ gr., morphine sulphate ¼ gr., and hyoscine hydrobromide 1/100 gr. Spinal anesthesia, consisting of Pontocaine 14 mg. and ephedrine sulphate 48 mg., was given at 8 p.m. between the L-2 and L-3 interspaces. During the operation, right after the peritoneal cavity was opened, respiration ceased at 8:24 p.m. Artificial respiration was started immediately and respiration returned at 8:52 p.m. Blood pressure and pulse remained at normal levels during this time.

An appendectomy was performed, and the patient was in deep coma when he was taken back to the ward. There was no response to usually painful stimuli. He showed frequent opisthotonic seizures and was markedly rigid. His neck was arched, as was his back. The upper limbs were in pronation and extension, and the lower limbs were rigidly extended. The patient continued in this state, showing frequent opisthotonic seizures, persistent rigidity, and fixed and dilated pupils. He died 57 hours after operation.

The abnormal findings at autopsy were limited to the brain. There were no gross abnormalities. Sections taken from various parts of the brain were fixed in a 10 per cent solution of formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin or by the Gros-Bielschowski technic for axis cylinders. Other blocks were fixed in alcohol, em-

bedded in collodion, and stained with toluidine blue. Sections cut from blocks fixed in formalin-ammonium-bromide were impregnated for astrocytes, and also for oligodendrocytes and microglia by the gold chloride sublimate and the silver carbonate technic, respectively.

The veins were considerably engorged and the endothelial cells of some of the blood vessels were moderately swollen. The perivascular and pericellular spaces were slightly increased in some areas, and there were cuffs of lymphocytes and pigment-laden cells around several blood vessels of the cerebral cortex, corpus striatum, and red nucleus (figure 1). There were diffuse degenerative changes of the nerve cells of all parts of the cerebral cortex (figure 2). The degeneration was manifested by pyknosis, loss of Nissl's tigroid substance, eccentration of nuclei, or vacuolation. The thalamus and corpus striatum showed degeneration to a lesser extent. Some nerve cells of the red nucleus had degenerated moderately (figure 1), although those of the substantia nigra were normal. Some nerve cells of the hypothalamus also showed degenerative changes, but other cell groups of the brainstem and also of the spinal cord appeared normal (figure 3). The most severe damage had affected the cerebellum, where not a normal Purkinje cell could be seen. Astrocytes and microglia were normal as were oligodendrocytes, except for an occasional example of acute swelling.

Comment: Cellular damage at the brainstem level (chiefly red nucleus) in this case was suspected clinically from the presence of opisthotonic seizures and from the fixed and dilated pupils. Although recovery may occur in patients showing either opisthotonic seizures or fixed and dilated pupils,*† serious sequelae may follow.[4,5] Courville,[4] for example, has reported a patient who, after ethyl-chloride-ether anesthesia, had fixed and dilated pupils and remained in coma for more than two days, then recovered. This patient, however, showed persistent blindness associated with optic atrophy. Moreover, she became mentally and physically deficient. In all likelihood, the complications of ether anesthesia, like those of nitrous oxide anesthesia, are due to asphyxia, as pointed out by Courville. Since the changes in the brain after cyclopropane anesthesia[6] are reported to be more or less identical with those following nitrous oxide anesthesia, asphyxia is probably the underlying mechanism of cerebral complications with this anesthetic agent as well.

The pathologic changes seen in our case, primarily involving the anatomically higher cerebral levels, were identical with those observed in a patient who had had repeated hypoglycemic attacks caused by an islet cell tumor of the pancreas. This patient died during one such attack, when coma preceding death lasted twenty-four hours. Her blood sugar at this time was 36 mg. per cent and although her blood sugar rose to 200 mg. per cent after the intravenous administration of glucose, there was no change in the coma. Irrversible degeneration had already occurred.

An interesting case described by Bailey[7] appears to fit into this group, even though the patient's pupils reacted to light. A woman of 48 years failed to recover consciousness after an operation for hyperthyroidism. Nitrous oxide anesthesia was used. "She lay quietly with eyes open and eyeballs wandering aimlessly. The pupils reacted to light . . . The arms were held rigidly in extension, the forearms pronated, wrists and fingers

*We have recently examined a two and a half year old child one hour after he developed cardiac arrest of uncertain duration during a thoracotomy for correction of a patent ductus arteriosus. He was in deep coma, his pupils were in mid-dilatation and fixed, and there were absent abdominal reflexes and extensor plantar responses. He died two hours and ten minutes after resuscitation from his cardiac arrest. The gross and microscopic examination of his brain showed no abnormality, doubtless because insufficient time had elapsed for histologic changes to become manifest.

†Critides and Browder have observed complete recovery of patients showing fixed and dilated pupils after evacuation of subdural hematomas.[3]

flexed. The legs were rigidly extended at knees and ankles. The tendon reflexes were hyperactive and there were bilatral Hoffmann and Babinski signs . . . The patient never gave any sign of recognition of her family or of other persons. The patient's clinical state seemed to us to be a typical akinetic mutism, but the electroencephalogram revealed no cortical activity at any time . . .

"The nuclear masses of the bulb, pons, midbrain, and hypothalamus were found to be intact with the exception of the mamillary bodies, whose nerve cells had disappeared and been replaced by gliosis. The caudate nuclei and putamen were softened, as was also the claustrum, but the globus pallidus was largely intact although there were a few macrophages and some of the large cells were swollen. The thalamus was not softened; its atrophy was due to secondary degeneration and gliosis such as follow decortication. The neocortex was universally softened; the picture being the familiar one of disappearance of the third, fourth, and fifth layers with myriads of macrophages. There was patchy degeneration also in the mesocortex of the anterior limbic region, in the agranular cortex of the posterior orbital region and of the anterior insular region, and in the juxtallocortex of the temporal lobe. The allocortex was intact.

"It is not at all likely that the defect of consciousness of this patient was caused by the softening of the putamen and caudate nuclei, and the atrophy of the thalamic nuclei is obviously secondary to the universal disaster of the neocortex. We have here, then, a clinical syndrome resembling that produced by lesions of the brainstem which has been produced by an anoxic degeneration of the entire neocortex."

GROUP 2A

Case 2. A 53 year old man was hospitalized on January 31, 1953 because of pulmonary tuberculosis, symptoms of which began with massive hemoptysis in November 1950. He improved after a right upper lobectomy was performed in March 1951. However, he became weak generally and developed fever about a year later, when roentgenograms of his chest revealed signs of a cavity in the right lower lobe. A right pneumectomy was done in May 1952. Two weeks later hemoptysis occurred. He has had intermittent fever since then and persistent right thoracic fistula.

On April 15, 1953 bronchoscopy revealed a bronchial fistula. Bronchoscopy was done again on May 18, 1953. At this time the fistulous opening was cauterized with sodium hydroxide and neutralized with acetic acid. The bronchoscope was withdrawn, and a few minutes later the patient coughed bloody sputum and showed respiratory stertor. Respiration then ceased and the patient lapsed into coma. An immediate tracheotomy resulted in return of spontaneous respirations after a period of apnea lasting approximately 20 minutes, during which a generalized convulsion occurred. Periodic convulsive twitchings of one part of the body or the other recurred. The patient was examined by one of us 24 hours later when he was in deep coma. The abdominal reflexes were absent and there were bilateral extensor-plantar responses. There were no other abnormal neurologic signs. Convulsive movements continued, as did the coma, and the patient died three days after the onset of his respiratory difficulty and coma. Postmortem examination of the brain was not done unfortunately.

Comment: The persistence of deep coma when the patient was examined neurologically 24 hours after its onset and the evidence of pyramidal tract damage were recognized as ominous signs. Severe pulmonary disease jeopardized whatever chances for survival there might have been otherwise.

Case 3. An obese 65 year old woman was hospitalized on April 27, 1953 because of symptoms indicating a gallbladder disease. On April 28, 1953 cholecystectomy was done. The preoperative medication consisted of Demerol 100

mg. and atropine sulphate 1/150 gr. She was given sodium Pentothal and ether anesthesia.

The operation was started at 7 a.m. At 7:15, 7:25, and 7:40 the patient was given 1.5 cc., 1.5 cc., and 2 cc., respectively, of curare intravenously in order to relax the abdominal musculature. The gallbladder was removed. At 8:42 a.m. respirations ceased during closure of the wound, although the pulse and blood pressure remained at normal levels. Pulse was 100 and blood pressure 150/90. The exact duration of apnea is uncertain, but it was estimated as at least several minutes. Respiration began soon after artificial respiration was started.

On returning from the operating room, the patient remained in deep coma. The pupils were in mid-dilatation, but they reacted to light. The only other abnormality on neurologic examination was extensor-plantar responses bilaterally. The next day she occasionally opened her eyes and swallowed. There was no response on usually painful stimulation. Her condition remained unchanged and she died on April 29, 1953.

Comment: The fact that this patient showed extensor-plantar responses and was unresponsive led us to believe that a considerable degree of cerebral degeneration had occurred. That these changes may be reversed was indicated by the fact that functional recovery, though not necessarily complete, has occurred in some such cases in our experience. With each succeeding day of continued unresponsiveness, however, the likelihood of satisfactory recovery lessened.

GROUP 2B

Case 4. A 55 year old thin, frail, right-handed housewife was hospitalized on January 2, 1944 because of attacks of severe intermittent pain over the right side of the face. General and neurologic examinations revealed no abnormality. A diagnosis of tic doloureaux of the trigeminal nerve was made. Her past health was good except that she had had pulmonary tuberculosis, said to have been arrested for several years by pneumothorax.

On January 3 a left trigeminal posterior rhizotomy was done under 2 gm. sodium Pentothal anesthesia in the sitting position. The preoperative medication was morphine sulphate ¼ gr. and hyocine hydrobromide 1/150 gr. The operation went smoothly, without appreciable drop in blood pressure. The patient was placed in a semi-sitting position after operation, and her nurse left the room for a few minutes. On her return the patient's head was sharply flexed, respirations were stertorous, and she was deeply cyanotic. The day after operation, the patient opened her eyes, moved all extremities in response to painful stimuli, but showed no other responses. She did not talk and gave no evidence of comprehension. There were bilateral ankle clonus and extensor plantar responses. She had been given picrotoxin 1 cc. intravenously several times in the 24 hours since operation without any appreciable change in her condition.

On January 5, 48 hours after operation, her condition remained unchanged except that ankle clonus had disappeared, but the extensor-plantar responses persisted. The patient frequently opened her eyes and looked around, but did not respond at all except by movement on painful stimulation.

On January 17 spontaneous movements of the limbs appeared and the patient seemed more alert, but otherwise there was no change. She was able to take nourishment beginning 48 hours after operation. On February 5 her condition was unchanged, except that she cried and laughed without provocation. Occasionally she opened her eyes or attempted to put out her tongue on command. She was discharged from the hospital on March 17, 1944.

The only abnormalities on neurologic examination, aside from inability to talk or understand, were absence of sensation over the left side of the face, absent corneal reflex on the left, and failure of frank flexor response on plantar stimulation. She moved her extremities only on painful stimulation.

This patient slowly regained the ability to speak by May 1944. She understood conversation to some extent but tired easily, and her vocabulary remained severely restricted (50 to 75 words), although she showed some voluntary, purposeful movements. She was unable to walk, feed herself, or control urination or defecation. She died of "pneumonia" nine months after operation. There was no postmortem examination.

Comment: This tragic case illustrates the importance of constant bedside attendance of a patient in coma. The respiratory obstruction and cyanosis that occurred during the nurse's brief absence doubtless resulted in cerebral asphyxia and irreversible cerebral damage. The patient's healed pulmonary tuberculosis may have been a predisposing factor in producing cyanosis and the severe cortical damage.

It is of considerable interest that some degree of speech and comprehension returned as late as four months after operation and that there was steady improvement until the occurrence of pulmonary complications. This sequence emphasizes the need for continued reeducation of such patients and indicates the favorable possibilities of restoring function.

Case 5. A 36 year old well-developed and well-nourished man was hospitalized on November 24, 1945 with a history of right lower quadrant pain.

On December 26 he was taken to the operating room for appendectomy. The preoperative medication consisted of Nembutal ½ gr., morphine sulfate ¼ gr., and hyocine hydrobromide 1/150 gr. This medication was given between 1:00 and 1:30 p.m. The anesthetic was started at 3:15 p.m. The anesthetic consisted of cyclopropane, oxygen, and ether. During the course of operation, respirations ceased for an uncertain period. The patient otherwise showed no alarming signs or symptoms during the operation, which took about two hours.

The patient awakened about 12 hours after operation, but was confused. Confusion and disorientation persisted for about 72 hours, during which time there were periodic generalized convulsive seizures, at times accompanied by spasms of opisthotonus. Neurologic examination was quite normal otherwise, except that the plantar responses were not as promptly flexor as normally.

The patient was discharged from the hospital on January 18. At that time he had been free from seizures for a period of ten days. He was well-oriented, although he was slow in understanding and answering questions. Moreover, he had no recollection of events for approximately one week prior to operation. The other striking abnormality on neurologic examination was ataxia on finger-nose test and heel-knee-tibia test and marked swaying in the Romberg position. Position sense of fingers and toes was impaired and both plantar responses were not as promptly flexor as normally.

The patient was next seen on February 26, 1946, when he complained of difficulty in seeing since operation. Comprehension and speech were slow. There was diminished visual acuity, so that he could not read newsprint. He made errors in counting fingers. There was marked ataxia on finger-nose-finger and heel-knee-tibia tests. He veered to one side or the other in walking. When objects were placed in his hands he failed to recognize them, and position sense of fingers and toes was very faulty. The left plantar response was not as promptly flexor as the right.

The patient was re-examined July 7, 1953. He showed some improvement, but he still could not read ordinary newsprint and had lost much of his initiative and drive. Gait was only slightly unsteady. Position sense of fingers and toes was normal, as were the finger-nose-finger and heel-knee-tibia tests. The left plantar response remained abnormal. He stated that he had not been able to work since his hospitalization because of general weakness, unsteadiness, and forgetfulness.

Comment: The mental confusion and the other abnormal neurologic findings in this patient were not as serious omens as prolonged unconsciousness would have been. The visual, stereognostic, and coordination defects in this case substantiate the belief of some observers that corresponding visual and sensory parts of the cerebral cortex and the cerebellar cortex are the most vulnerable to anoxia. The lesser degree of susceptibility of the motor cortex in this case is indicated by the absence of muscular weakness and relatively slight abnormality of the plantar responses. The part of the cerebral cortex that bears the brunt of the anoxic insult, however, ap-

pears to vary to a considerable extent. There were no signs of defects referable to lower phylogenetic levels—basal ganglia or brainstem or peripheral nerves—at any time.

GROUP 3

Case 6. An obese 47 year old woman was hospitalized on June 1, 1953 with a clinical diagnosis of uterine fibroids. On June 5, under caudal epidural xylocaine anesthesia combined with nitrous oxide and oxygen, a dilatation and curettage, supravaginal hysterectomy, and left salpingo-oophorectomy were done. Three cc. of 2 per cent xylocaine were injected at 1:50 p.m. At 1:55 p.m., 17 cc. of xylocaine were injected. Ten minutes later the level of anesthesia was T-8, but the patient still could move her legs. Dilatation and curettage was started at 2:10 p.m. and completed at 2:30, when she was put in the Trendelenburg position. An abdominal incision was made at 2:30 p.m. Sodium Pentothal 0.48 per cent (ten drops per minute) was started at 2:30 and the peritoneal cavity was opened at 2:30.

The patient started to strain during the procedure, so that the rate of flow of Pentothal was increased. Oxygen and nitrous oxide inhalation anesthesia was then started. Her straining ceased, but respirations became obstructed for "a few minutes." One cc. of curare was given intravenously at 2:55 p.m. because of poor relaxation of the abdominal wall. The respiratory obstruction, attributed to laryngeal and bronchial spasm, reappeared.

At 3:10 p.m. blood pressure was unobtainable and pulse could hardly be felt. Atropine sulphate 1/25 gr. was given intravenously at 3:15 p.m. The blood pressure returned to 190/70 and the pulse was 80. Respirations improved. Sodium Pentothal and nitrous oxide were discontinued at 3 p.m., after which oxygen had been administered. At 3:35 p.m. the surgeon found the operation difficult because of poor relaxation of the abdominal wall. Therefore 1 cc. of curare was given intravenously at 3:35 p.m. and another ½ cc. was given at 3:40 p.m. The patient's respiration became very shallow. She was put in the horizontal position at 4:10 p.m. Respiration then became normal.

The operation was completed at 5 p.m., when the blood pressure was 140/90, pulse 96, and respirations 20. The patient did not awaken until the next morning, when she was very torpid and confused. Speech was difficult to understand.

The vital signs were at normal levels, and neurologic examination showed no abnormality. At 5:15 that evening, about 24 hours after completion of the operation, the patient's mental state cleared. She was oriented and her speech was normal. The neurologic examination was normal except for retrograde amnesia for a period of about a week before operation. Gradually memory for events that had occurred during the week before operation returned, and when seen last on June 19, 1953, about two weeks after operation, she recalled all events right up to the time when she was taken to the operating room. She also recalled events after her awakening the day after operation.

Comment: We have seen a considerable number of such cases, some with cardiac arrest, in which the awakening from anesthesia is moderately delayed and associated with mental confusion and amnesia, but without other abnormal neurologic signs. Full recovery has invariably occurred in these patients.

Although this patient may be considered as having suffered from mild lack of oxygen, she did not show the following combination of signs that, when present together rather than individually, "almost invariably" denote oxygen want, according to Lucas:[8,9] "increased respiratory rate and dyspnea, increased heart rate, restlessness and delirium, and sweating and pallor."

DISCUSSION

It is interesting that the first two cases in group 2 who did not survive showed rather prolonged coma, whereas the other two patients of this group (cases 4 and 5), who survived but showed serious sequelae, awakened within 24 hours after operation. All of these patients showed abnormal neurologic signs. Coma that is prolonged beyond two or

three days after asphyxia signifies a grave prognosis. Fox's patient, who finally recovered completely from cardiac arrest of 27 minutes due to proved ventricular fibrillation, could be aroused from coma ten hours after resuscitation. Our observations on the prognostic significance of coma agree in general with those recorded by Courville[10–12] in his excellent study of 13 cases of asphyxia following nitrous oxide anesthesia. In another publication[4] Courville described a patient who developed cyanosis and cardiac failure after ethyl chloride-ether anesthesia and was in coma for more than two days. She survived, but was totally blind and retarded mentally and physically.

The anesthetic agents in the reported cases varied, the common factor to all cases being respiratory arrest or obstruction. Cyanosis did not occur in all of the patients, testimony to the fact that its absence does not mean an absence of asphyxia, since the one may occur without the other.[13] Doubtless cerebral anoxia accounted for the neurologic complications of all these cases.

Clinical as well as experimental evidence[14,15] proves that there is a gradient of susceptibility of the brain to asphyxia, anoxia, and ischemia. The phylogenetically higher cerebral levels, that is, those more recently developed, are most vulnerable to oxygen lack. The vulnerability lessens as one descends these functional levels of the brain to the brainstem and spinal cord. Accordingly, the abnormal neurologic signs appear in a rather orderly fashion, first referable to the newer portions of the brain and then descending through the various phylogenetic layers. This progress of symptoms results from the greater resistance of the old parts of the brain to oxygen lack. The greater resistance of the old parts of the cortex to oxygen lack is interestingly shown in Bailey's case,[7] in which the allocortex (archicortex and paleo cortex) was intact although all parts of the isocortex showed neuronal degeneration. By studying electrical activity, Sugar and Gerard[16] have also demonstrated a progressive depression from the cortex to the medulla during anoxia. This same gradient of reaction holds for hypoglycemia, the clinical and pathologic manifestations of which are indistinguishable from those of anoxia. In fact, these two essential requirements for cerebral metabolism are synergistic, so that high blood sugar levels have been shown to counteract the effects of anoxia, just as inhaling oxygen counteracts the adverse effects of hypoglycemia.[2]

The hypothesis formulated as a guide to prognosis in cases of asphyxia depends on this gradient of vulnerability of the nervous system to anoxia. When there are signs of dysfunction of the brainstem, such as opisthotonic convulsions and fixed and dilated pupils, recovery has not occurred in our experience. One might anticipate severe degeneration of nerve cells of the cerebral and cerebellar cortices, globus pallidus, putamen, thalamus, and midbrain (such as occurred in case 1). Similar pathologic changes were found in a case of hypoglycemia secondary to an islet cell tumor of the pancreas.

In patients (group 3) whose only abnormal neurologic sign immediately after the episode of asphyxia is prolonged unconsciousness, either followed or not followed by memory disturbances, minor and varying reversible degrees of damage to the superficial cerebral levels may be postulated. Such patients show full

functional recovery within a relatively short time (a few days to a few weeks). According to Cobb,[17]* the "nerve cells of the cerebral cortex will stand about three minutes of complete anoxia before irreparable damage is done. The large Betz cells can withstand somewhat more. The large nerve cells of the spinal cord can stand 15 minutes of anoxia. In the brainstem and cerebellum the time is somewhere between these two." That there is some variation in the effects of anoxia is shown by case 1 in which the Purkinje cells of the cerebellum were the most severely damaged of all cells.

The presence of other abnormal neurologic signs, such as extensor-plantar responses, impaired vision, ataxia, or astereognosis, although not inconsistent with survival or full recovery, are usually accompanied by some neurologic sequelae, lessening gradually with the passage of time. These may be quite serious, as in our second patient, who remained mentally and physically defective.

Among the residual symptoms that may occur after recovery from the anoxemic state are mental and emotional disturbances, motor symptoms (convulsions, paralysis, rigidity, tremor, and incoordination), and sensory changes (impaired vision and stereognosis), depending upon the area of the brain that bears the brunt of the anoxic insult.

The more prolonged the unconsciousness is, the more guarded must the prognosis be. Courville's extensive experience with asphyxia[10] after nitrous oxide anesthesia led him to say that "the persistence of coma . . . during the second and third days are ominous." Our experience with asphyxia in general agrees with this viewpoint. There are no sharp boundaries between the three groups of cases described, further experience with which may lead to their subdivision, depending on the patient's course of progress. Doubtless age will have to be considered as an important factor in foretelling the degree of recovery after asphyxia. Our criteria for recovery are based upon observations in patients in the fourth, fifth, sixth, and seventh decades of life. The possibilities of recovery increase as one descends the age scale. Windle[20] has clearly shown that the fetus and the newborn are much more resistant to deficiency in their oxygen supply than is the adult. Doubtless asphyxia in newborn infants is a common cause of severe later disturbances. Obstetricians should understand this. Some of Windle's animals, although of perfectly normal outward appearance, were dullards. Windle[20] says, "We are prone to blame inferior human mentalities on poor environment and especially on defects of the germ plasm. It is probable that asphyxiation at birth is partly responsible in man, as it was in our guinea pigs."

The importance of re-education procedures in furthering recovery in the borderline cases of asphyxia (group 2) must also be stressed.

Lucas[9] states that "the earliest change that occurs in the anoxic brain cell is an intracellular edema." His own earlier histologic studies[8] in animals and man, however, make no mention of such an early change. This "earliest change," as yet unproved, forms the basis for the treatment of cerebral anoxia by dehydration with concentrated human serum

*Neurophysiologic studies in our laboratory,[18] as well as in other laboratories, have demonstrated a differential sensitivity of spinal cord structures to lack of oxygen. Our studies, in conjunction with histologic ones on chronic surviving preparations from other laboratories, show that practically no ganglion cells can recover from about one hour of complete ischemia of the spinal cord.[19]

albumin.[21] One cannot yet evaluate the results of this treatment.

CONCLUSIONS

Neurologic examination of patients who have suffered from respiratory arrest or obstruction occurring during or immediately after operation may provide important clues to prognosis. Our own experience with such cases has led to the following conclusions, which would appear to apply to patients suffering from cardiac arrest or anoxia from other causes.

1. The occurrence of fixed and dilated pupils and generalized extensor rigidity indicates a severe irrecoverable degree of neuronal damage at the brainstem level, and is, in our experience, incompatible with survival. The appearance of either fixed and dilated pupils or marked generalized extensor rigidity alone is of very grave prognostic significance. Such patients may survive, but serious sequelae may appear.

2. Delayed awakening from anesthesia or asphyxia without abnormal neurologic signs other than mental confusion or impaired memory indicate mild reversible damage at a superficial cortical level and full recovery may be expected.

3. Prognosis is less certain in the intermediate group of patients who show abnormal motor or sensory signs. Survival usually occurs in these patients, and, although there may be recovery which may continue for months, serious sequelae, such as impaired mentality or vision, ataxia, motor or sensory abnormalities, may persist. However, coma that is prolonged more than two or three days is of very serious significance and is often followed by death or serious neurologic after-effects.

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Spontaneous Subarachnoid Hemorrhage

Clinical and Therapeutic Factors Affecting Prognosis

Joseph F. Rowley, M.D., James F. Sullivan, M.D. and Louis L. Tureen, M.D.

THE INCIDENCE of spontaneous subarachnoid hemorrhage observed in general hospitals is comparatively high, and the 30 to 50 per cent mortality rate accompanying such catastrophes justifies an earnest search for definitive therapeutic procedures in an attempt to decrease these figures. Despite the advent of cerebral angiography and the impetus this has given to the surgical treatment of such accidents, there are conflicting opinions among neurologists and neurosurgeons about the optimal procedures, and, more important, the time for intervention.[1–13] The present study of a sizeable series of patients with spontaneous subarachnoid hemorrhage was undertaken in the hope of throwing some light on these issues. In this investigation an attempt was made to correlate the prognosis with the clinical picture, and to consider in retrospect which patients might have benefited by modifying our concepts of treatment. We were particularly interested in examining the interval between the onset of symptoms and the most advantageous utilization of surgical procedures, with special reference to the interval before death or the occurrence of subsequent hemorrhages. We were also concerned with the prognostic significance of 1) the presenting symptoms, 2) the symptoms and physical findings developing during the hospital course, and 3) the varying systemic disorders which accompanied or were the precipitating cause of the subarachnoid hemorrhage. Finally an analysis was made of results of the conservative therapeutic procedures employed. From these data and a review of the most recent literature, it is hoped that some inferences may be drawn as to the indications for angiography, surgery, and the timing and selection of such procedures.

MATERIAL

The 157 cases selected for this study were from the neurologic and neurosurgical services of St. Louis City Hospital and the St. Louis University Hospital group. The former represented primarily indigent patients, the latter private patients. These cases were collected from admissions between the years

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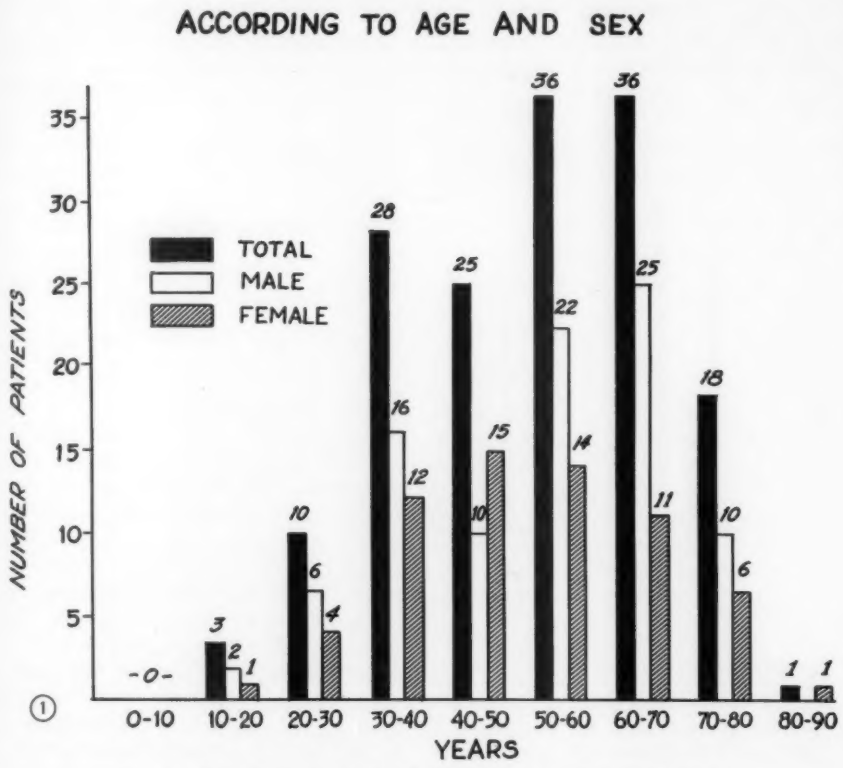

FIG. 1. Incidence of spontaneous subarachnoid hemorrhage according to age and sex.

1945 to 1955, but are thought to represent only a portion of the patients suffering from spontaneous subarachnoid hemorrhage. Most of the cases excluded were rejected because of incomplete data. Many patients admitted in profound coma and manifesting bloody spinal fluids died shortly after entry. Since, in most instances, we could not be certain whether or not these patients suffered intracerebral and/or intraventricular hemorrhages, they were not considered suitable for inclusion in our statistics.

The cases selected for this study were as follows: 1) 29 patients in whom the diagnosis of subarachnoid hemorrhage was confirmed at autopsy; 2) 16 cases with history of subarachnoid hemorrhage and in whom cerebral aneurysms were confirmed by angiography; and 3) 112 patients with classic symptoms of subarachnoid hemorrhage (sudden onset of headache, coma, or confusion followed by nuchal rigidity, with transient or no localizing neurologic signs, and bloody and/or xanthochromic spinal fluid at the time of examination).

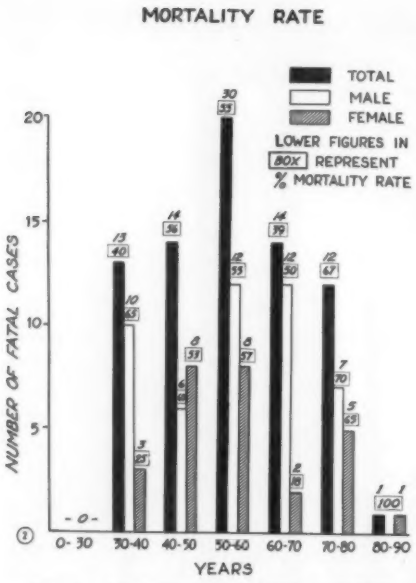

FIG. 2. Spontaneous subarachnoid hemorrhage mortality rate.

INCIDENCE OF MORTALITY

The over-all mortality for the 157 patients was 74 or 47.2 per cent. Only 9 per cent of the cases were under age 30 and none of these died. The largest number of cases were between 30 and 60 years of age (89 cases); their mortality rate of 52.8 per cent was only slightly higher than that (47.2 per cent) for the 55 patients who were over 60. After the third decade, incidence in the various age groups (figure 1) is relatively constant. When a comparison of the two sexes is made, a significant difference is readily apparent (figure 2). In all age groups, more men were affected than women. The over-all mortality rate for males was 52.2 per cent, for females 40 per cent. In the 30 to 60 year group, the death rate was 61.2 per cent for men, as compared with 42.5 per cent for women; in the over 60 year group, the mortality rates were 51.4 per cent for men and 45 per cent for women.

TABLE 1

PRESENTING SYMPTOMS

Symptom	*Number of Patients*	*Percentage*
Coma	69	44
Headache	49	31
Disorientation and confusion	22	13
Acute alcoholism	3	2
Hemiplegia	3	2
Hypertension	2	1
Convulsions	3	2
Eclampsia and pre-eclampsia	3	1.5

PRESENTING COMPLAINTS AND CLINICAL COURSE

Initial symptoms and presenting complaints are listed in table 1, and the frequency of symptoms during the course of illness in table 2. A total of 69 patients (44 per cent) were *comatose;* some had been found unconscious or were seen to collapse. There were 16 other patients who were conscious when first examined at the hospital, but subsequently lapsed into coma. Other disturbances of consciousness were manifested by 22 patients: confusion, disorientation, and bizarre behavior. Initially unconscious and disoriented patients comprised 57 per cent of the series. This group could contribute little toward providing a history.

TABLE 2

INCIDENCE OF SYMPTOMS DURING COURSE OF ILLNESS

Symptom	*Number of Patients*	*Percentage*
Headache	89	57
Nausea	28	18
Vomiting	44	28
Visual disturbance	29	18
Dizziness	14	8
Coma	85	54
Convulsions	29	18
Hemiplegia	11	7

Headache was reported in some of the comatose patients, either before losing consciousness or after they had become sufficiently alert to make complaints. A total of 89 patients complained of headache, 49 on admission, 40 after regaining consciousness. This symptom generally subsided during the first week. Headaches preceding the subarachnoid hemorrhage for months or years were reported in 38 per cent. No consistent prodromal pattern was established.

Nausea, vomiting, and dizziness appeared as a constellation of symptoms in a group of patients. The symptoms of nausea and dizziness required sufficient consciousness for the patient to perceive and complain of the symptoms. This was not true of vomiting which occurred in 44 patients, some of whom were obtunded or semicomatose at the time. These symptoms were generally present at the onset of the hemorrhage and did not persist over 48 hours.

Visual symptoms were reported in 29 cases, but the lack of detailed descriptions made this finding valueless for interpretation in this series.

A variety of symptoms were present in the remainder of the cases, including convulsions and eclamptic and preeclamptic states. Hemiplegia[14] of varying degree and duration appeared in 26 patients. The spinal fluid was bloody and xanthochromic in 137 patients, xanthochromic without fresh blood in 17 others. No record of spinal puncture was noted in three.

Spinal fluid pressure readings were determined in all but 24 patients. Of these, 14 with unmeasured spinal fluid pressure were in coma at the time of examination and subsequently died. It is probable that difficulties were encountered in measuring the very high pressure in many of these. Normal pressures of less than 150 mm. of water were found in 29 patients, borderline pressures (150 to 200 mm.) in 12 patients, and elevated pressure (over 200 mm.) in 89 patients. A mortality rate of 48.9 per cent was yielded by the 49 patients with pressure over 300 mm. When certain symptoms are considered in conjunction with the elevated pressure, a direct correlation between spinal fluid pressure rise and mortality was established. In comatose patients with spinal fluid pressures over 300 mm., the mortality rate was 58 per cent; those with pressures under 300 mm. manifested a mortality rate of 45 per cent. Similarly, those with symptoms of headache, nausea, vomiting, and dizziness with pressures over 300 mm. showed a mortality rate of 55 per cent, whereas those with pressure under 300 mm. and with the same symptoms had a mortality rate of 38 per cent.

CONCOMITANT PHYSICAL DISORDERS

In table 3 are listed concomitant physical disorders present in 85 cases (55 per cent) in our series of spontaneous subarachnoid hemorrhage.

Hypertension. This symptom was manifest by 52 patients with a mortality rate of 57.7 per cent (figures 3 and 4).

TABLE 3

CONCOMITANT MAJOR DISEASES IN PATIENTS WITH SPONTANEOUS SUBARACHNOID HEMORRHAGE

Associated Disease	*Number of Patients*	*Deaths*
Hypertension	52	30
Syphilis	7	2
Diabetes	5	0
Laennecs's cirrhosis	3	2
Blood dyscrasia	3	2
Arteriosclerotic heart disease	4	3
Postpartum	6	1
Other	5	4
Total	85	44

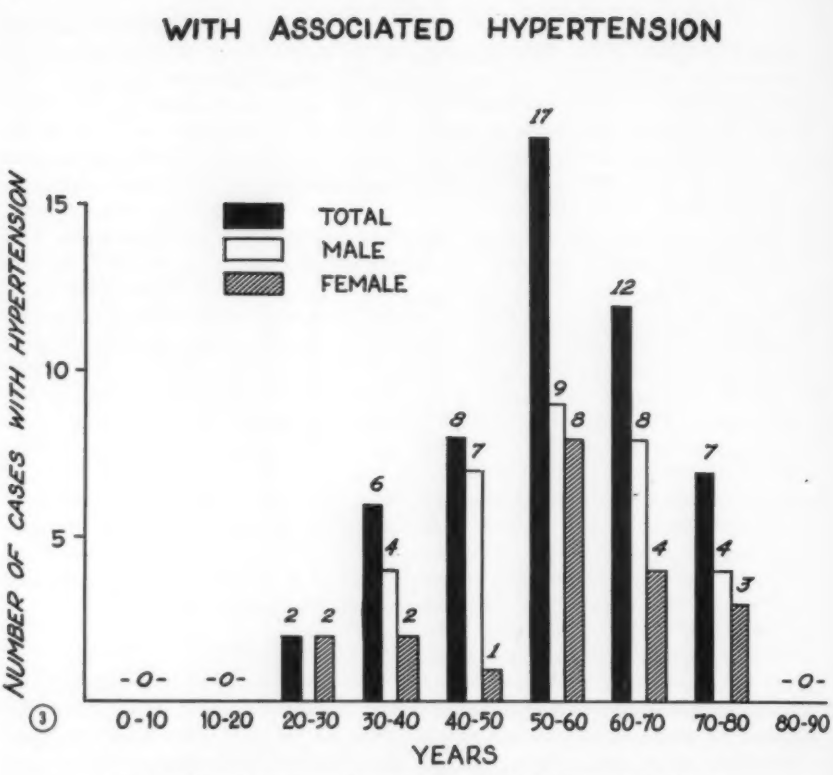

FIG. 3. Incidence of spontaneous subarachnoid hemorrhage with associated hypertension.

The mortality rate is significantly higher in males than in females (73 per cent as compared to 42.3 per cent). The highest death rate occurred in the 30 to 60 age group for both men and women, 78.5 per cent and 47 per cent respectively. In the over 60 age group, the mortality rates were 67.7 per cent for men and 42.9 per cent for women. These data raise the question whether or not antitensive drugs would be of value in the medical management of such cases. We have no significant information to report. In the few cases in which such drugs were tried, no particular benefit was apparent. A larger series of case studies employing these agents would be necessary before valid conclusions could be drawn. Reports from surgical clinics dealing with aneurysms indicate they are of value in decreasing bleeding during operations.[15,16]

Postpartum spontaneous subarachnoid hemorrhage. There were six cases in our series. The symptoms and diagnostic findings appeared during the first week following delivery. In four patients symptoms developed during the first

two postpartum days. Of these patients two were eclamptic, one was pre-eclamptic. There was one death among this group, occurring on the tenth day, following an episode of re-bleeding. The cause of the subarachnoid bleeding was explained in none of these patients. Attention has been drawn to this postpartum complication recently.[17,18]

Syphilis was present in seven cases, diabetes in five, and congestive heart failure in four. These conditions seemed to bear no causal relationship to the subarachnoid hemorrhage. In three patients with Laennec's cirrhosis and three with blood dyscrasias, a generalized bleeding tendency was present and it is believed this was responsible for the subarachnoid bleeding. Walton's work on subarachnoid hemorrhage of unusual etiology elaborates this aspect.[19]

ANGIOGRAPHY

Angiograms were performed on 30 patients (19 per cent of the total series). Aneurysms were detected in 13 patients, multiple aneurysms in one patient, and arteriovenous malformations in three. Normal arterial patterns were established in 12 patients. Results were unsatisfactory in two patients. None of the angiography was performed during the critical period alluded to earlier. Thus, in 53 per cent of those patients subjected to this procedure, angiographic evidence of cerebral artery malformation was established. In addition, autopsies were obtained in 29 patients, or 39 per cent of those who died. In these, 15 patients demonstrated ruptured aneurysms, a figure remarkably close to those detected by angiography. Subarachnoid hemorrhage was noted in all cases. Although it is probable that the incidence of cerebral aneurysms is considerably higher,[20,21] our data have not confirmed it.

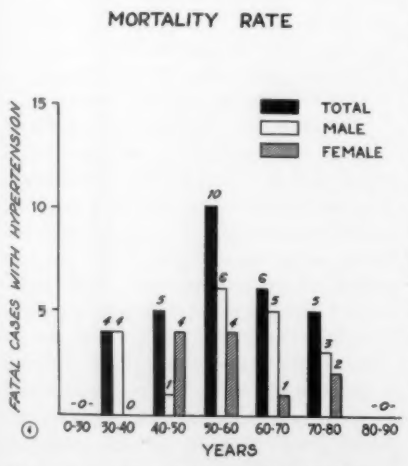

FIG. 4. Spontaneous subarachnoid hemorrhage with associated hypertension mortality rate.

SURGICAL INTERVENTION

A total of 11 patients underwent some type of surgical attack upon the source of bleeding. Of these, six had common carotid artery ligations; with only one exception, an aneurysm had been demonstrated by angiography prior to ligation. In one case ligation was without complication, but the patient died during a subsequent direct attack upon the aneurysm. After termination of the initial bleeding, the remaining five were discharged with minimal neurologic impairment. Of these, two had further subarachnoid hemorrhage, one at three years with recovery and one at five years which was fatal. One patient had an internal carotid artery ligation without further bleeding or neurologic sequelae at the time of discharge.

The number of patients undergoing carotid artery ligation is too small to allow comparison with the group in

TABLE 4

RESULTS OF SURGICAL INTERVENTION

Age	*Sex*	*Aneurysm*	*Hypertensive*	*Time of Follow-up*	*Result*
32	F	yes	no	3 years	No recurrence
37	F	yes	no	1 year	No recurrence
15	M	yes	no	4 months	No recurrence
20	F	no	no	3 years	Re-bled after 3 years—lived
66	M	yes	yes	5 years	Re-bled after 5 years—died
57	F	yes	no	8 days	Died after carotid ligation during direct attack on aneurysm
			INTERNAL CAROTID LIGATION		
43	F	yes	no	none	No sequelae at discharge
			DIRECT ATTACK ON ANEURYSM		
22	M	yes	no	1 year	No sequelae
32	M	yes	no	none	No sequelae
47	M	yes	no		Died postoperatively
55	M	yes	no		Died postoperatively
57	F	yes	no		Died postoperatively

which no surgery was done. Moreover, all ligations were carried out during the third and fourth weeks of hospitalization at a time when the greatest danger had passed.

Direct attempt to trap the aneurysm at time of craniotomy resulted in death in the immediate postoperative period in three of the five patients in whom this procedure was employed. The remaining two survived without sequelae. The age, sex, surgical procedure, follow-up, and results appear in table 4. The adverse influence of hypertension is again noted, since the only patient having a fatal recurrence after carotid artery ligation was hypertensive.

Analysis of these few cases indicates that carotid artery angiography in the convalescent phase is a safe procedure as to immediate mortality, that it seems to be effective in preventing the early re-bleeding, and that neurologic sequelae to common carotid ligation are minimal under these conditions. The reports of Dowling and Falconer[3, 22–24] indicate that this procedure is particularly beneficial in the acute phase.

Figure 5 shows that 55 patients died during the first week of hemorrhage and ten during the second; thus, 87.9 per cent of the deaths occurred during this critical interval. Figure 6 represents the number of deaths during each day of the first week. Since 82 per cent of the deaths occurred during the first four days, this interval would appear to be the critical span. These figures establish the fact that, if surgical intervention is to decrease the mortality rate, operation during this critical phase is essential.

The need for definitive measures is further demonstrated by the analysis of eight cases in whom it was quite evident that there had been re-bleeding after the initial hemorrhage. In each of these patients, after the initial attack, signs and symptoms of improvement were interrupted by signs and symptoms of further bleeding (table 5). In all but one of these patients the re-bleeding occurred within the first week, and death followed in from one to four days. In an additional group of eight patients who suffered re-bleeding after discharge from the hospital, six survived the second at-

TABLE 5

SIGNIFICANCE OF RE-BLEEDING

Age	Sex	Hypertension	Day of Recurrence	Result
During Initial Hospitalization				
36	M	no	7	Died 9th day
74	M	no	2	Died 4th day
63	M	no	4th week	Died
70	M	yes	3	Died
41	F	yes	5 and 7	Died 11th day
71	M	no	3	Died
44	M	no	6	Died 8th day
70	M	yes	3	Died
After Discharge Following Initial Bleeding				
			Interval from Discharge	
66	F	no	2 years	Lived
66	M	yes	1 month	Lived
17	M	no	21 months	Lived
70	F	no	1 month	Lived
65	M	no	1 month	Lived
42	F	yes	2 years	Died
66	M	yes	4 years	Died
52	F	no	8 months	Lived

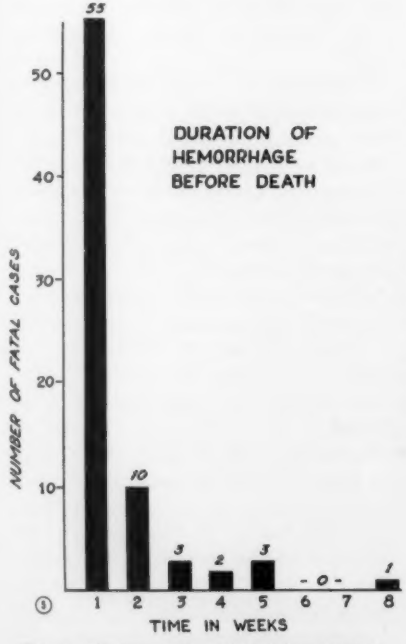

FIG. 5. Duration of hemorrhage before death in spontaneous subarachnoid hemorrhage.

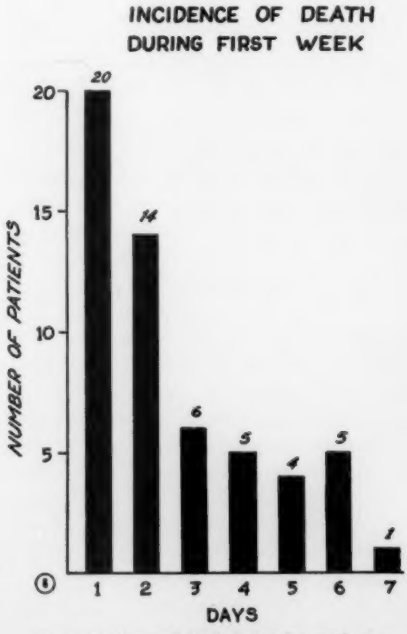

FIG. 6. Incidence of death during first week after spontaneous subarachnoid hemorrhage.

tack. Of these episodes four occurred within the first year, three within two years, and one after four years. The deaths occurred in the patients with the longest interval following the first attack.

FOLLOW-UP OF PATIENTS SURVIVING FIRST ATTACK OF SUBARACHNOID HEMORRHAGE

Of this series, 52.8 per cent or 83 patients survived the initial attack of subarachnoid hemorrhage. It was possible to obtain follow-up case histories in 46 survivors (55 per cent) for variable periods ranging from three months to ten years. Recurrent hemorrhages occurred in eight patients in from one month to two years after leaving the hospital (average of three patient years). Of these patients, two died. During the follow-up period, 38 patients suffered no further hemorrhage (table 6). This incidence is encouragingly low. The mortality rate in this series from repeated subarachnoid hemorrhage is contrary to one report in the literature,[25] but comparable to that in a more recent paper.[26]

DISCUSSION

It must be noted at the outset that, in the light of recent work, justifiable criticism can be leveled at the paucity of surgical interference in our series of cases. This study represents an evaluation of our concepts and practices in an effort to improve them. The immediate consequences of this study should result in our adoption of practices which, in the main, involve earlier definitive, diagnostic, and therapeutic measures. The 50 per cent mortality rate, it seems, could and must be lowered. This conclusion is apparent in the current literature on the subject.[23,24,27] Since 78 per cent of the fatalities occurred during the first week and 36 per cent of them during the first day, early intervention is necessary. The eight patients who suffered a second hemorrhage during the first week warn us against complacency with the apparently convalescent patient.

TABLE 6

FOLLOW-UP ON PATIENTS SURVIVING FIRST HEMORRHAGE

83 of 157 survived—(Follow-up available on 45 of these).

Time	*Number*	*Re-bleeding*	*Result*
0 to 3 months	5	3	All lived
3 to 6 months	5	0	
6 to 12 months	6	1	Lived
1 to 2 years	7	3	1 died
2 to 3 years	7	0	
3 to 4 years	5	1	Died
4 to 5 years	2	0	
5 to 6 years	2	0	
6 to 7 years	1	0	
7 to 8 years	1	0	
8 to 9 years	3	0	
9 to 10 years	1	0	
Total	45	8	2 fatal

Consideration of definitive therapeutic measures is governed by the fate of these people. Analysis has already indicated that early symptoms failed to give adequate prognostication for the consequences of the first attack. We feel all early cases must be considered surgical emergencies. Once the diagnosis of spontaneous subarachnoid hemorrhage is established, what course is to be followed?

Angiography is the diagnostic tool which is currently most helpful. Objections against the morbidity from this procedure must be weighed against the advantages of early localization of aneurysms. Perese and co-workers[28] indicate a morbidity of approximately 3 per cent from the use of Diodrast. This has been reduced by the utilization of other contrast media as recently reported by Smolik.[29] In clinics where angiography is performed within the first 72 hours of onset of the hemorrhage, no deteriora-

tion of the clinical status of the patient has been reported.[22,26] Present advocates of early angiography insist that the procedure be performed as soon as the vital signs of the patient are stabilized, certainly within the first three days.

Following the identification and localization of the vascular lesion, the choice of surgical procedure must next be considered. Following are the three principal operative technics which have been advocated: [26,30–37] 1) ligation of the homolateral common carotid artery, 2) ligation of the homolateral internal carotid artery, and 3) direct approach to the aneurysm or malformation in an attempt to trap or remove it. Falconer[23] reported a series of 50 cases using one or a combination of the above. There was an 18 per cent mortality rate (nine cases); 33 patients survived without sequelae, while eight had neurologic deficits, of whom five nevertheless were gainfully employed. From the experience of Dowling and others, it would seem that the first method carried the lowest mortality rate, the last the highest. On the contrary, Logue,[26] employing direct ligation on anterior cerebral artery lesions, reported a surgical mortality as favorable as that cited by authors using the carotid ligation technic. As a result of this study, we feel that ligation of the common carotid artery is indicated as soon as the aneurysm is localized. Any subsequent intracranial approach for the direct surgical attack on the aneurysm must depend on other factors. Thus, the choice of surgical procedure utilized will depend upon the experience of the individual operator.

Patients who present several weeks to months following subarachnoid bleeding pose a different problem. In view of the favorable prognosis noted in the follow-up group and the low mortality in those who re-bled, it is felt that conservative management is in order. Patients in whom the hemorrhage was due to a concomitant disease (cirrhosis, blood dyscrasias, and so on) generally are managed medically, with emphasis on the underlying disorder. On the other hand, male hypertensives in the 30 to 60 age group and comatose patients with marked spinal fluid pressure elevation would appear to have the gravest prognosis.

SUMMARY AND CONCLUSIONS

1. The mortality rate in a series of 157 cases of spontaneous subarachnoid hemorrhage was 48 per cent, with a higher rate in the male.

2. The early presenting signs and clinical course were not found to be prognostic of the ultimate outcome of the hemorrhage.

3. Patients with spontaneous subarachnoid hemorrhages are to be regarded as surgical emergencies.

4. In view of the high mortality rate during the first week, it is recommended that angiography be performed within 48 hours of the onset of the hemorrhage, to be followed by common carotid artery ligation when the aneurysm is located.

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Determination of Retinal Artery Pressures in Diagnosis of Carotid Artery Occlusion

Albert Heyman, M.D., Herbert R. Karp, M.D. and Byron M. Bloor, M.D.

ALTHOUGH determinations of retinal artery pressure by ophthalmodynamometry were first made 50 years ago, the use of this technic in neurologic and ophthalmologic practice has been limited. The disturbances in vision associated with spontaneous thrombosis of the internal carotid artery have aroused new interest in the circulation of the retinal vessels,[1,2] and measurement of retinal artery pressures has been suggested as a means of determining the patency of the carotid circulation. Since determinations of retinal artery pressures have been made in only a small number of patients with proved impairment of the carotid circulation,[3–5] its value as a diagnostic procedure has not been fully established.

This report presents experience with retinal artery pressure determinations in patients with occlusion of the carotid artery produced either by spontaneous thrombosis or by surgical procedures. In addition, the effects of manual compression of the common carotid artery on the retinal artery pressures in control subjects are presented. The usefulness and limitations of ophthalmodynamometry as a means of determining occlusive disorders of the carotid artery are also discussed.

METHODS

The instrument used in this study was the Bailliart ophthalmodynamometer, which consists of a spring-loaded plunger, the movements of which are transmitted to a dial indicating pressures from 10 to 150 grams of water. The metal tip of the plunger is applied to the lateral surface of the sclera and the retinal vessels are observed by direct ophthalmoscopy. Care is taken to apply the instrument with its long axis in the horizontal plane to avoid adding the weight of the instrument to the pressure reading (figure 1). The first appearance of pulsations of a large branch of the central retinal artery represents diastolic pressure. The subsequent disappearance of pulsation with increased pressure on the sclera indicates systolic pressure. Although the entire procedure may be performed by a single individual, it has been found more convenient and ac-

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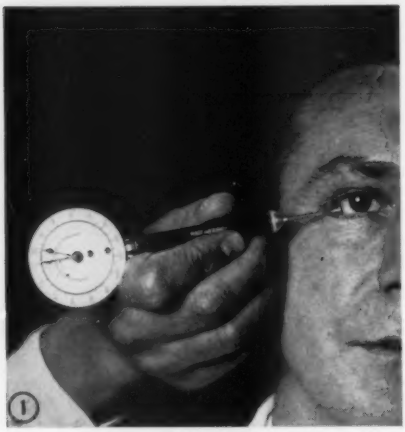


FIG. 1. Position of ophthalmodynamometer on sclera.

curate to have one person observe the retinal artery pulsations and another to apply the instrument and note the pressure readings. Mydriatics are generally used, but local anesthesia is not necessary. The examination is carried out with the patient in a supine position. At least two and usually three measurements are made in each eye, depending on the constancy of the readings. An effort is made to obtain the readings in rapid succession in order to avoid alterations in intraocular pressure which might result from prolonged compression of the globe. The average of these readings is used in comparing the retinal artery pressures in the two eyes.

RESULTS

The subjects in this study were divided into five groups. The first group consisted of 16 subjects in whom there was vascular disease with neurologic evidence suggesting carotid artery occlusion. Carotid arteriograms performed in 14 of these patients demonstrated either narrowing or complete occlusion of the internal carotid artery. The results of retinal artery pressure determinations are shown in table 1. The mean decrease in diastolic and systolic pressures in the ipsilateral eye was 27 and 30 per cent, respectively. In general, the differences in retinal artery pressures in the two eyes were not as marked in the group with partial occlusion. In some

TABLE 1

RETINAL ARTERY PRESSURES IN PATIENTS WITH IMPAIRED CAROTID CIRCULATION

Patient	Degree of Carotid Occlusion	Diastolic			Systolic		
		Patent	Occluded	Per Cent Decrease	Patent	Occluded	Per Cent Decrease
G.H.	Partial	59	53	10	150	127	15
B.R.	Partial	55	40	27	105	73	31
S.McG.	Partial	65	35	46	140	89	36
V.G.	Partial	73	37	49	>150	124	>18
J.T.	Partial	70	70	0	125	96	22
O.M.	Partial	86	86	0	>150	136	> 9
L.M.	Partial	60	34	43	>150	74	>50
E.S.	Complete	78	32	59	105	40	52
T.J.	Complete	79	48	39	143	74	48
M.P.	Complete	58	45	22	140	95	32
S.M.	Complete	75	72	4	138	117	15
J.J.	Complete	72	57	21	117	87	26
D.W.	Complete	91	76	17	>150	118	>21
D.Y.	Complete	45	29	36	101	55	46
T.G.	No data	30	26	13	100	63	37
B.G.	No data	41	22	46	125	51	59

> Indicates pressures greater than calibration of ophthalmodynamometer.

FIG. 2. Arteriogram in patient (O.M.) showing narrowed carotid lumen below origin of ophthalmic artery. Diastolic retinal artery pressures were equal; systolic pressure was slightly decreased on ipsilateral side.
FIG. 3. Arteriogram in patient (J.T.) showing multiple areas of narrowing at carotid bifurcation. Diastolic retinal artery pressures were equal; systolic pressure was decreased on ipsilateral side.

of these patients (figures 2 and 3) arteriography revealed the lumen of the internal carotid to be only slightly narrowed, and a major reduction in retinal artery pressures is not to be expected in such individuals.

Arteriographic evidence of carotid artery occlusion was not obtained in two of the 16 patients. One of them (T.G.) was thought to have aortic dissection with involvement of the carotid vessels, while the other (B.G.) had worsening of hemiparesis and aphasia following accidental perivascular infiltration of contrast medium in an attempted carotid arteriogram. In both patients pulsations over the internal carotid were absent and there was an associated hemiplegia. Both the systolic and diastolic retinal artery pressures in these patients showed a very striking decrease in the eye ipsilateral to the carotid occlusion.

The second group consisted of four patients with intracranial aneurysms whose carotid circulation was gradually occluded by a Crutchfield clamp. Retinal artery pressures were determined prior to application of the clamp and on successive days as the common carotid was narrowed by tightening of the clamp. At the time of surgical exposure of the common carotid artery, the mean intraarterial pressure distal to the clamp was determined before and after complete closure of the vessel. The clamp was then partially opened, and the number of turns of the screw required to produce the observed change in arterial pressure was determined. The subsequent degree of occlusion of the carotid artery could then be estimated as a function of the number of turns on the screw. The results of this study are presented in figures 4 and 5. In each of the four patients, gradual narrowing of the carotid artery was accompanied by a progressive fall in retinal artery pressure in the ipsilateral eye. A slight increase

TABLE 2

RETINAL ARTERY PRESSURES IN PATIENTS WITH SURGICAL LIGATION OF CAROTID ARTERY

Patient	Diastolic			Systolic			Effects of Ligation
	Patent	Ligated	Per Cent Decrease	Patent	Ligated	Per Cent Decrease	
H.P.	87	56	36	>150	84	>44	None
G.C.	68	55	19	140	90	36	Hemiplegia
M.McD.	66	38	42	105	77	27	Hemiplegia
W.R.*	80	76	5	150	150	0	None
L.W.*	58	46	21	108	89	18	None

* Patients with partial ligation.
> Indicates pressures greater than calibration of ophthalmodynamometer.

in retinal artery pressure was consistently noted in the contralateral eye. In one patient (E.K.) an unexpected rise in pressure was noted in the ipsilateral eye two days following the application of the clamp. It was later learned that the clamp had been released during the previous evening.

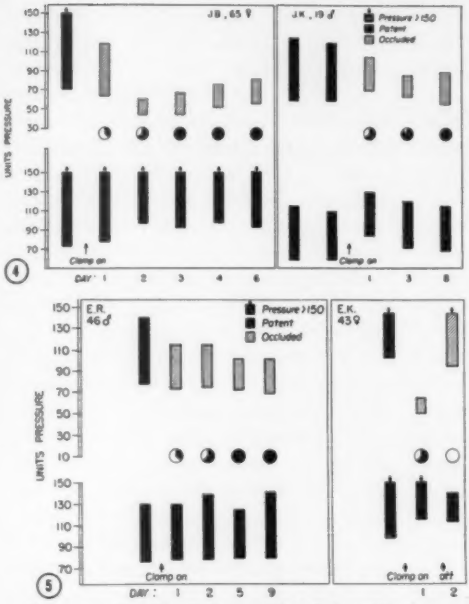
The third group consisted of five patients in whom the carotid circulation had been interrupted by ligation in the neck for a few months to as long as four years previously. All but one of these patients showed a significant decrease in the ipsilateral retinal artery pressure (table 2). In this patient (W.R.) arteriography revealed that the ligated vessel had not been occluded completely. There appeared to be some correlation between the development of neurologic deficit consequent to carotid ligation and the degree of reduction in retinal artery pressures.

Retinal artery pressures were determined in a fourth group which consisted of seven young male subjects without neurologic or vascular disease. The determinations were carried out before and during manual compression of the common carotid artery sufficient to obliterate the pulsation in the corresponding superficial temporal artery. In each of these subjects this maneuver produced a significant fall in retinal artery pressure in the ipsilateral eye. Following release of carotid compression, the retinal artery

TABLE 3

RETINAL ARTERY PRESSURES IN SUBJECTS WITHOUT EVIDENCE OF IMPAIRED CAROTID CIRCULATION

Patient	Diastolic			Systolic		
	Right	Left	Per Cent Difference	Right	Left	Per Cent Difference
Young Subjects without Cerebral Vascular Disease						
J.W.	62	60	3	98	95	3
E.C.	75	76	3	138	129	6
T.C.	65	67	3	127	117	8
J.B.	55	45	18	100	100	0
S.V.	65	64	2	110	116	5
D.S.	60	60	0	100	110	9
F.C.	71	65	8	131	122	7
Patients with Normal Carotid Circulation Demonstrated by Autopsy or Arteriography						
H.A.	58	59	2	115	127	9
G.M.	52	62	16	95	106	10
H.M.	105	110	5	150	150	0
J.K.	58	54	7	115	110	4
E.R.	78	76	3	138	129	6
J.B.	70	73	4	150	150	0
H.P.	67	61	10	116	113	2



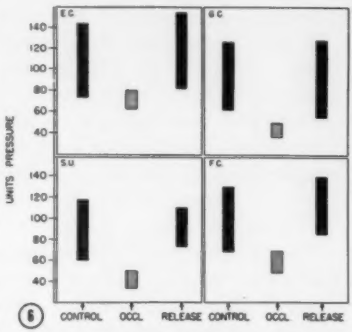


FIG. 4. Changes in retinal artery pressure during gradual occlusion of common carotid by Crutchfield clamp. The circle represent the estimated degree of narrowing of the carotid lumen. The upper series of bars represents pressures in the eye on the side of the carotid occlusion. The lower series represents pressures in the other eye.

FIG. 5. Changes in retinal artery pressure during gradual occlusion of common carotid artery by Crutchfield clamp. The circles represent estimated degree of narrowing of the carotid lumen. The upper series of bars represents pressures in the eye on the side of the carotid occlusion. The lower series represents pressures in the other eye.

FIG. 6. Effect of manual compression of common carotid artery on retinal artery pressures in control subjects.

pressures returned to normal. The contralateral eye showed no change in pressure measurement. The results of four such determinations are shown in figure 6. These seven patients were presumed, on the basis of their ages and the absence of neurologic and vascular symptoms, to have normal carotid circulations. They were considered as control subjects, along with seven others in whom the carotid vessels were found to be intact by arteriography or autopsy examination. Bilateral measurements of retinal artery pressure in this group of 14 controls showed remarkably equal values (table 3). Only two subjects had a difference of diastolic pressure greater than 15 per cent. A larger group of control subjects was not studied, since previous reports have shown that the retinal artery pressures in normal individuals are equal.[5]

The fifth group consisted of 38 elderly patients who were confined to state mental institutions and domiciliary Veterans Administration hospitals because of hemiplegia or dementia thought to be caused by cerebral vascular disease. Retinal artery pressures were measured in these patients in an attempt to detect previously unsuspected carotid artery thromboses. This study was largely unsuccessful, since only 17 of this group were able to cooperate sufficiently to permit visualization of their retinal vessels. Only one of the 17 had a significant difference in retinal artery pressures. This individual ironically had no

neurologic signs and had been hospitalized because of severe rheumatoid arthritis. However, he gave a history of a transient episode of numbness of the contralateral hand, and palpation of the carotid artery on the side of the lowered retinal pressure revealed no pulsation.

DISCUSSION

The use of the ophthalmodynamometer as a method of assessing the patency of the internal carotid artery is based on several anatomic and physiologic observations. In man the blood supply to the retina is derived from the ophthalmic artery, a direct branch of the internal carotid. An interference of the blood flow in the internal carotid artery, therefore, would be expected to result in a reduction of pressure in the ophthalmic and retinal arteries, unless there were an adequate collateral circulation by way of the circle of Willis or through anastomoses from the external carotid system. Thus, observations of the pressure in the retinal vessels may often provide information as to the adequacy of the blood flow in the ipsilateral carotid artery.

The pulsations of the retinal arteries in the normal state are not usually visible. Progressive increase in intraocular pressure will result first in the appearance of venous pulsations. Later, as the intraocular tension rises to equal diastolic pressure, collapse of the retinal arteries occurs in diastole and pulsations of the vessels become visible. A further increase of intraocular pressure to overcome that of systolic pressure causes a collapse of the retinal arteries and the arterial pulsations cease. Thus, by applying a known incremment of pressure to the sclera and observing the retinal artery with an ophthalmoscope, the eye functions as a sphygmomanometer, reflecting the pressure in the vessels supplying the ophthalmic artery. The results of this study are reported as that increment of pressure (grams of water) which, when added to the intraocular tension, produces and then obliterates pulsations in the retinal artery. The basic assumption is made that impairment of the internal carotid circulation produces no significant alteration in the resting intraocular tension of the ipsilateral eye. This was borne out by tonometric determinations in four patients with proved carotid artery occlusion. Other factors which might influence the values obtained by this method are the size of the globe, the compressibility of the sclera, and the changes in intraocular pressure produced during the determination.[6] It has also been suggested that displacement of the globe, which sometimes occurs during this procedure, may produce sufficient angulation of the ophthalmic artery to reduce significantly the pressure in the retinal vessels.[7] The effect of these factors is minimized by the fact that the comparative determinations are carried out rapidly by the same observer and under as nearly similar conditions as possible.

Much has appeared in the ophthalmologic literature regarding the use of these basic principles in arriving at absolute values for pressure within the retinal arteries.[8] The wide range of published figures attests to the inadequacy of this method as a precise determination. The average retinal artery pressure obtained by this technic has been found to be 30 to 45 mm. Hg diastolic and 65 to 75 systolic, that is, approximately half of the systemic blood pressure.[8] Direct manometric pressures in the cat eye have shown that the pressure in ophthalmic

arteries is 95 per cent and that in the retinal arteries 70 per cent of mean aortic pressure.[7] Accurate direct measurements in the human eye are not available.

Although the height of the retinal artery pressure depends largely upon the systemic blood pressure, we have observed only one individual in whom the systemic pressure was too great to obtain readings by ophthalmodynamometry. It has been suggested that the brachial artery pressures should be determined at the time of examination of retinal artery pressures.[5] This seems to have little merit as a routine procedure, since a difference in brachial artery pressures does not detract from the significance of a difference in retinal artery pressures. It may, however, disclose the presence of an aortic arch syndrome or an innominate artery thrombosis in which the circulation in both the brachial artery and carotid artery is impaired. Bilateral occlusion of the carotid arteries is not uncommon in the aortic arch syndrome, and the retinal artery pressures of both eyes may be too low for satisfactory comparison. The method used in this study is a comparison of the pressures in one eye with that of the other, and its validity is based on the assumption that the circulation in one carotid artery is relatively intact.

The degree of accuracy of ophthalmodynamometry may be reduced by minor errors in technic, some of which are worthy of emphasis. To allay apprehension, the procedure should be explained to the patient and application of the plunger to the sclera should be demonstrated prior to the actual determination. Care should be taken to avoid interpreting venous pulsations as representing diastolic pressure. Erroneous determinations of the systolic and diastolic end points are frequently made in patients with bradycardia or cardiac arrhythmia.

The degree of reduction in retinal artery pressure necessary to establish a diagnosis of carotid artery occlusion cannot be stated in absolute values. In a cooperative subject, however, in whom the exact time of appearance and disappearance of arterial pulsations can be accurately noted, a reduction of 25 to 30 per cent in both systolic and diastolic pressures is diagnostic of impaired carotid circulation. A similar reduction in either the diastolic or systolic pressures should be considered as confirmatory data in patients with the clinical picture of carotid artery disease.

Some workers have recommended that only the diastolic pressure be used as the diagnostic criterion, since the appearance of arterial pulsations can be more accurately determined than their disappearance.[4] In our experience, both systolic and diastolic pressures are of value, since some patients with impairment of the carotid circulation showed a decrease in systolic retinal artery pressure only. This was particularly true in patients with incomplete occlusion or with slight narrowing of the vessel.

Retinal artery pressures have been found to correlate well with direct carotid pressure readings at the time of surgical ligation,[9] and ophthalmodynamometry has been suggested as a means of estimating the degree of collateral circulation following ligation of the carotid artery. We do not, however, believe that this procedure can be depended upon to determine the extent of the decrease in cerebral circulation following carotid ligation or to predict in

which cases ligation would be safe. It should be noted, however, that, of the ten patients in this study with complete surgical or thrombotic occlusion of the internal carotid artery, only one (S.M.) failed to show a significant reduction in the ipsilateral retinal artery pressure. Long-term ophthalmodynamometric observations of patients with carotid ligation might provide useful information as to the appearance and degree of collateral circulation following this procedure. Such a study is in progress.

Despite the unsatisfactory results obtained in our survey of senile patients with hemiplegia and dementia, we believe that such a study should be repeated. The use of local anesthesia and mydriatics and more careful selection of cooperative patients might provide information of value as to the incidence of carotid thromboses in this age group.

The only complication we have encountered with this procedure was a mild subconjunctival hemorrhage in one individual following application of the instrument. We are not unmindful, however, of the possibilities that retinal detachment and thromboses of the retinal vessels may follow prolonged or too vigorous pressure on the sclera. Such complications must be extremely rare, however, and to our knowledge have not been reported. Despite these potential hazards, we believe that measurement of retinal artery pressure is sufficiently valuable to warrant its use as a diagnostic method.

CONCLUSIONS

Ophthalmodynamometric measurements of retinal artery pressure were obtained in control subjects and in various groups of individuals with impairment of the carotid circulation. Patients with arteriosclerotic narrowing or occlusion of the internal carotid artery showed significantly lower retinal artery pressures in the ipsilateral eye. Surgical ligation or gradual occlusion of the carotid artery also produced measurable alterations in the ipsilateral retinal artery pressures.

These studies indicate that measurement of retinal artery pressures is a useful procedure in establishing the diagnosis of carotid artery occlusion. It may also be of value in interpreting the results of surgical interruption of the carotid vessels.

We are indebted to Dr. Barnes Woodhall and Dr. Guy L. Odom for permitting us to study their patients.

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Seizure States and Pregnancy

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THE EFFECT OF PREGNANCY on seizure states has received little attention in recent medical literature. When mentioned it has been mainly to point out the difference between the convulsions of eclampsia and those of "idiopathic" epilepsy.[1–3] McClure[4] recently reported a group of 20 patients with grand mal type seizures, the majority of whom had more frequent attacks during pregnancy. In 1946 Bennet[5] reported 16 cases and reviewed the literature to that date. He concluded that the effect of pregnancy on frequency of seizures was unpredictable, but only one of the cases he reported was improved during pregnancy.

Even less has been reported about seizure states with onset during pregnancy, the only recent report being that of Boshes and McBeath.[6] Though Bennet[5] quotes Zangemeister to the effect that 2 per cent of eclamptic patients develop epilepsy and mentions other single case reports, Dieckmann,[7] in his recent book on the toxemias of pregnancy, refers to epilepsy following eclampsia as a rarity.

Further study of the effect of pregnancy on seizure states was suggested by the following observations:

First, previous studies had demonstrated that certain patients with seizure states showed clinical improvement and recorded improvement in their electroencephalogram when treated with a moderately low sodium diet plus sodium-binding ion exchange resins.[8] Since increased retention of sodium and water is common during pregnancy, similar treatment appeared indicated in the pregnant woman with seizure states.

Second, it appeared that more women with seizure states are marrying and having children. This is a natural result of improved drugs for controlling seizures, plus realization on the part of both the patient and the physician that most seizure states are not due to heredity and that, even in those where heredity is a factor, the chance of transmitting clinical seizures to the child is not great.[9] This means that the problem of the proper management of the woman with a seizure state during pregnancy will become increasingly frequent in medical practice, and studies to deter-

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mine the best form of treatment are necessary.

Third, we were impressed by the number of patients who reported that their seizures first occurred during pregnancy. In some patients this was associated with definite eclampsia, but in others no serious complication was present.

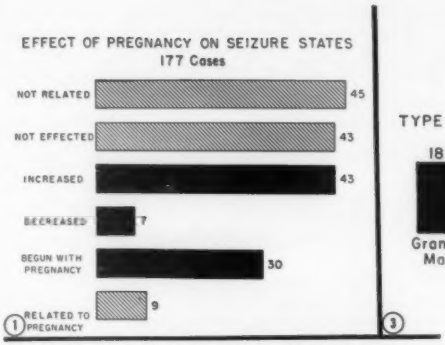
STATISTICAL SUMMARY

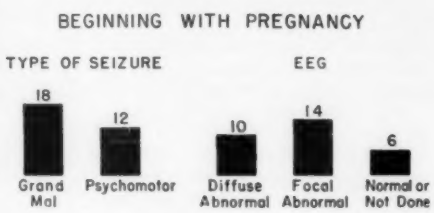
We have reviewed 1,650 cases seen under the Seizure Control Program in the State of Virginia during a 15 month period. Of these, 490 were women over 14 years of age and 177 of these women had been or were pregnant. A study of these 177 women (figure 1) showed 45 in whom the seizure state was not related to pregnancy. Most of these were older women in whom seizures occurred a number of years after their last pregnancy as a result of other known causes such as trauma, tumor, or cerebral vascular accident. In 43 cases there was no evidence that pregnancy had any effect on the seizure state. In 43 cases seizures were definitely increased, either in frequency or severity or both during or immediately after pregnancy. In 30 cases the first seizure was reported to have occurred during pregnancy. Only seven patients reported that they had a decrease in severity and frequency of seizures during pregnancy. In nine cases, although the seizure state did not begin during pregnancy, there were indications that some complication of pregnancy might have been a factor in causing the condition which began later.

A further study of the 43 patients with seizures increased by pregnancy is shown in figure 2. Of these, 29 had predominantly grand mal type seizures and 14 had psychomotor type seizures. No patient with petit mal seizures associated with pregnancy was observed during the period of this study, but in the past we have seen one patient with typical petit mal seizures in whom the attacks disappeared during pregnancy and recurred between pregnancies. One patient in this study had only petit mal seizures as a child and these stopped with onset of menstruation at age of 13. She has now experienced four grand mal type seizures, two occurring during the month following delivery with each of her two pregnancies. Attacks were predominantly nocturnal in 14 of these cases, and 19 patients reported that attacks had been more frequent around the time of menstruation. In only four was the increase in seizures during pregnancy related to a definite toxemia.

Analysis of the 30 cases beginning during or immediately after pregnancy is shown in figure 3. In 18 patients attacks were grand mal in type, and in 12 they were psychomotor in nature. In nine patients seizures increased during menstruation, and 12 had a majority of nocturnal attacks. Toxemia of pregnancy was present in 14 of these cases and appeared definitely related to the onset of the seizure state. Of these 14 patients, nine had psychomotor seizures with a temporal lobe focus demonstrated on electroencephalogram. In general, focal electroencephalographic abnormality was more common in patients whose attacks began with pregnancy (46.5 per cent) than in those whose attacks were more frequent during pregnancy (20 per cent).

The nine cases listed as having onset related to pregnancy were women whose recurring seizures began anywhere from three months to five years after a severe complication of pregnancy, most of them having had eclampsia, and in whom





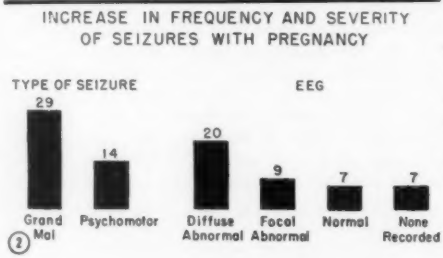


FIG. 1. Effect of pregnancy on seizure states in 177 cases.

FIG. 2. Increase in frequency and severity of seizures with pregnancy.

FIG. 3. Incidence of seizures beginning with pregnancy.

careful search could reveal no other cause such as head trauma, heredity, and so on. Of the seven cases who were benefited during pregnancy, five gave a definite history of more adequate treatment with anticonvulsant drugs than they had had previously and this, rather than the pregnancy, appeared to be the factor which caused an improvement in their condition. One of these, however, had attacks occurring usually during menstruation, and her attacks stopped completely during pregnancy but recurred when menstruation was resumed.

CASE REPORTS

The following six cases are presented to demonstrate various aspects of the effect of pregnancy on patients with a seizure state:

Case 1. This woman was 14 years old when she was first seen in one of the field clinics operated by the University of Virginia Seizure Control Clinic. At that time she gave a history of grand mal type attacks, first appearing when she was 13 years of age. She was placed on a combination of Dilantin and phenobarbital and had no further attacks for two years.

She was seen three years later (1949) when she was 17 years old because of a recurrence of generalized convulsions. Physical and neurologic examinations at that time were negative. An electroencephalogram performed on a day when she had had three generalized convulsions showed almost continuous three to four per second high amplitude waves which at times showed spike and waves and of three per second frequency.

From 1949 to March 1953 this patient was carried on a combination of Dilantin and Mebaral or Mesantoin and Mebaral. When seen in March 1953, the patient reported that her attacks had been controlled for two years. She had completed high school without further episodes; she married and was pregnant at the

time of her next clinic visit. She was taking only Mebaral at that time. Special advice concerning the necessity of minimum weight gain and importance of noting any edema formation was sent to her referring physician. It was also recommended that she resume Mesantoin 0.1 gm. twice daily, in addition to Mebaral.

The patient was not seen again until after her delivery. At that time it was reported that, despite efforts on the part of her physician to advise her about diet, she ignored this and gained a total of 40 pounds during pregnancy. She was never started on Mesantoin, as advised, and in fact her anticonvulsant was decreased early in pregnancy. About half-way through pregnancy she experienced a recurrence of grand mal type seizures. At about eight months she had an episode of severe convulsions which caused her to be admitted to the hospital for three days. Although the attacks were controlled temporarily, no serious attempt to reduce edema and weight gain was made. No fetal heart sounds were heard following this episode. Two weeks later another episode of frequent generalized convulsions developed and the patient was admitted to the hospital, where she delivered a stillborn infant. Following delivery she continued having generalized convulsions fairly frequently for approximately three months. At that time the originally advised adequate doses of anticonvulsant drugs were prescribed, and since then she has been free of seizures for three years. An electroencephalogram done in 1955 showed only a mild, diffuse abnormality consistent with a lowered seizure threshold. Although this patient and her husband have been advised that she probably could now go through a normal pregnancy with careful supervision, the husband steadfastly opposes this because during her first pregnancy others advised that she should never become pregnant again. The events of this pregnancy are represented in figure 4.

Case 2. This woman was 16 years old when she was first seen in the Seizure Control Clinic at the University of Virginia Hospital in 1951. She gave a history of an illness during the second month of life which resulted in partial paralysis of the right leg and the left arm. The patient had been told that this was an attack of poliomyelitis. She first began to have seizures when 13 years of age. When first seen at 16 years of age, her attacks were occurring two or three times a month and were both psychomotor and grand mal in nature. Most of her attacks occurred at night. An electroenecphalogram done in February 1951 was reported as abnormal and showing nonspecific dysrhythmia.

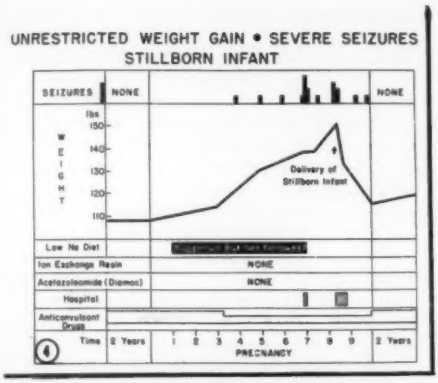
From 1951 until April 1955 the patient was treated with phenobarbital and Dilantin, and at times she had periods of three or four months without any attacks. She repeatedly failed to take her medication and then attacks recurred, coming on in groups of two or three at a time. The attacks were often associated with her menstrual period.

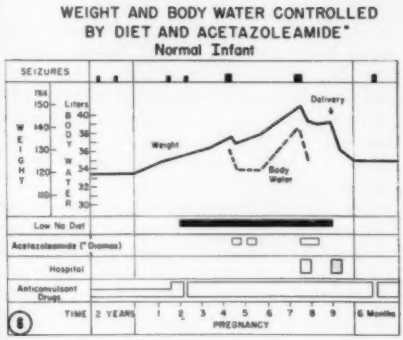
When seen in April 1955 she was four months pregnant and had gained 10 pounds. During pregnancy she had begun having much more frequent seizures, having them daily and at times having them two or three times a day. According to her report, she had increased Dilantin to 0.5 gm. a day without effect. A repeat electroencephalogram showed a right temporal lobe spike focus and there was also some diffuse abnormality. She was brought into the hospital and put on a low-caloric, low-sodium diet, combined with an ion exchange resin (Resodec) 15 gm. three times a day; Dilantin was reduced to 0.4 gm. per day. On this regimen her seizures stopped and she lost six pounds.

She was discharged from the hospital on the same regimen, except for reduction of Resodec intake to 15 gm. twice a day to be taken for a two-week period. She experienced two seizures in May, and after that had no more attacks during the rest of her pregnancy. Nevertheless, despite instructions about her diet, when seen one month from term, she had gained 25 pounds and showed slight evidence of edema. Accordingly she was hospitalized again, and once again on a low-sodium diet and Resodec her weight was reduced 11 pounds in a three-week period. She had no attacks and delivered a normal infant.

Body water determinations were not obtained until after the second course of weight reduction was begun, but these, as compared with a postpartum total body water study, showed total body water to be increased. The events of this pregnancy are shown in figure 5.

Case 3. This woman was 18 years old when she became pregnant. She had been seen in the Seizure Control Clinic at the University of Virginia Hospital since the age of nine. As a child she had several generalized convulsions which occurred between the ages of three and six,





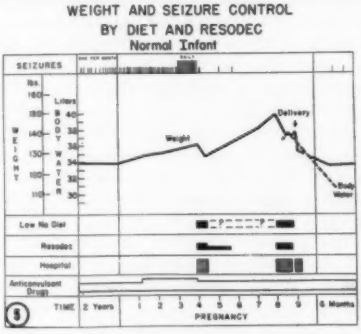


FIG. 4. Events of pregnancy in case 1.

FIG. 5. Events of pregnancy in case 2.

FIG. 6. Events of pregnancy in case 3.

and she began to have grand mal type seizures again at the age of nine. These had continued since that time, occurring about once a month, until she was given medication. Attacks occurred only occasionally thereafter, usually when she omitted her medicine. She had had two generalized seizures during the two years before she became pregnant, and it was suspected that both of these had occurred when she missed taking her anticonvulsant medication.

This patient worked as a maid in the hospital and was a regular attendant at the Seizure Control Clinic. From the beginning of her pregnancy, she was followed closely by the Seizure Control Clinic and the Obstetrics Clinic with advice concerning restriction of weight gain and regularity of medication. She had one attack when only six weeks pregnant and at that point her anticonvulsant medication was increased. She had another attack during the third month when she missed medication. During the fifth month of her pregnancy she was seen because of two generalized seizures and it was found that she had gained six pounds since her last clinic visit. She was put on a low-sodium, low-caloric diet and given Diamox. The first ten-day course brought about a weight loss of four pounds and a similar course was repeated the next month. Body water studies done before and after the first course of Diamox showed a reduction in total body water from 36.2 to 34 liters.

During the eighth month of pregnancy she again gained weight excessively and had three seizures in two days. At that point she had gained a total of 30 pounds since the onset of pregnancy. At that time she was hospitalized

and put on a strict diet and Diamox, with a resulting weight loss in one week of seven pounds; once again a reduction of total body water from 38.8 liters to 34.2 liters occurred. She did not gain weight again before term and delivered a normal infant without any attacks. Since delivery, which was six months ago, she has had one attack which occurred when she missed medication. The events of this pregnancy are shown in figure 6.

Case 4. This woman was 14 years old when she was first seen in the Seizure Control Clinic at the University of Virginia Hospital. She gave a history of frequent seizures since the age of 18 months, when she had suffered a severe attack of whooping cough complicated by pneumonia and had generalized seizures with unconsciousness lasting for two or three hours. During her early childhood she had several generalized but not severe convulsions a day, lasting only 13 to 30 seconds and associated with tonic flexion of the arms and legs. As she grew older they became less frequent, but occurred in groups of two or three about once a month. They were often nocturnal and often associated with menstrual periods.

When this patient was seen again in 1953, she continued to have seizures about once a month. At this time she was 18 years of age. Some of these seizures were rather severe, although most of them occurred at night, and on numerous occasions she had had a dislocation of her left shoulder.

Because of the seizures she had stopped school when she was 15 years old and had led a very restricted social life. She had become discouraged about medications and had taken practically no medication for two years.

The original electroencephalogram done in 1950 showed a borderline tracing with more slow activity than could be considered normal and suggesting cortical dysfunction of a diffuse nature. There were no focal discharges or abnormalities.

Beginning in May 1953 this patient was put on 0.1 gm. Dilantin and 32 mg. Mebaral four times daily. On this medication her seizures were controlled for over a year until she was seen again in July 1954. During this period her social life had expanded and discussion of possible marriage came up. Since her seizure state apparently was the result of a severe episode of whooping cough, probably with encephalitis, and since there was no family history of seizures, she was advised there was no contraindication to marriage. She was warned that, if she married and became pregnant, her case should be followed carefully to prevent recurrence of attacks if possible. This patient married and became pregnant in October 1954, at which time her attacks had been controlled for 18 months. During the first three months of pregnancy she gained only six pounds, but she had three generalized seizures, all coming on at night.

During this patient's pregnancy she was placed on a low-caloric and low-sodium diet most of the time, with the addition of extra phenobarbital to her medication and the addition of Diamox to her regimen when she showed spurts of weight gain. Despite the best advice of our clinic and of her physician, she gained a total of 25 pounds during her pregnancy. On several occasions she had gains of four or five pounds within a period of two or three weeks, resulting each time in severe seizures. She had a normal labor and delivery. Following delivery in May 1955, the patient had eight attacks during the following five months, but with further increase in medication her attacks have been controlled for six months.

This patient's physician noted that she had a marked increase in attacks when she experienced spurts of weight gain. During the one month when she gained the most weight, she had eight seizures; otherwise they were not this frequent. She was not hospitalized for the control of her diet or weight.

Case 5. This woman was 26 years old when she was first seen in the Seizure Control Clinic at the University of Virginia Hospital on December 4, 1953. She gave a history of seizures beginning on January 1, 1952, associated with the birth of her first child, the actual convulsions coming on immediately after delivery and being associated with delirium. Following this she had attacks several times a week, which consisted of smelling a very bad odor, frothing at the mouth, and some facial movements without loss of consciousness. They continued very much the same until seven months following the delivery of her second child about seven years later, when, in addition to the bad odor and movements of the mouth, the patient became unconscious and also showed irrational behavior. During the past four years the patient had also experienced six generalized grand

mal convulsions, all coming on during sleep.

Physical and neurologic examinations were negative and the skull roentgenogram was negative. The electroencephalogram showed diffused abnormality with a strong focal emphasis in the right mid- and anterior temporal region.

The patient was diagnosed as having chiefly psychomotor but occasional grand mal seizures and adjustment in her medications was attempted. Seizures were less frequent and less severe but were never controlled on medication.

In April 1954 the patient was admitted to the Clinical Center of the National Institutes of Health at Bethesda, Maryland, where the presence of a right temporal focus was confirmed by repeated electroencephalogram tracings. On April 28, 1954 a right temporal lobectomy was performed and the operation was summarized as follows:

"Electrocorticographic abnormality was maximum in the second temporal convolution at the junction of the anterior and middle thirds. Gross objective abnormality was present in the form of sclerosis in the peri-insular gray matter, and to a marked degree at the tip of the right temporal lobe. The patient's aura was reproduced by deep stimulation in the first temporal convolution."

Following surgery, this patient had several seizures during the ensuing week and then was completely free of attacks for three months. Attacks then began to recur infrequently and, when placed on a combination of phenobarbital and Dilantin, her attacks were again controlled for a two or three month period. Since that time the patient has continued to have one or two attacks a month and was readmitted to the Clinical Center for further study.

Case 6. This woman was 17 years old and had been married six months when she was seen in the Seizure Control Clinic at the University of Virginia in August 1954. She gave a history of convulsive seizures occurring in association with measles as a young child and occurring again in association with a head injury when eight years old. Her seizures recurred and had continued regularly since the age of 13. They were usually psychomotor in nature, occasionally going on to a generalized convulsion. When examined the patient was on no anticonvulsant medication and was experiencing three to six attacks per week.

Physical and neurologic examinations were negative, but an electroencephalogram showed a definite focal change in the right mid- and anterior temporal areas.

She was placed on Dilantin 0.1 gm. twice daily and Mebaral 32 mg. four times daily. She was advised that, if she were to become pregnant, she should limit her weight gain and consult her physician about any necessary changes in anticonvulsant medication.

After starting medication this patient's attacks decreased to about one a month. Shortly following this she became pregnant and went through a normal pregnancy, during which she gained only 11 pounds. The delivery was normal and the child was normal. During a portion of her pregnancy attacks occurred only every six weeks, and early in her pregnancy Mebaral was increased to 64 mg. twice daily.

This patient was seen three months following pregnancy and reported that her attacks continued approximately one per month, though she had reduced Mebaral to half the dose taken during pregnancy. An electroencephalogram repeated at that time was reported as borderline normal though slightly slow, and even sleep revealed no further abnormality. The focal changes seen a year previously, before the patient was put on medication, were not present.

This patient stated she felt that pregnancy had improved her attacks, though it was clear that her improvement began with adequate anticonvulsant medication, and that the restriction of weight gain during pregnancy was probably an added factor in the good results.

DISCUSSION OF CASE REPORTS

These are only a few of the cases which have come under our observation. Case 1 is presented as an example of the severe results which may occur even in a mild seizure state when weight gain in pregnancy is completely unrestricted. Cases 2 and 3 are presented to show the effectiveness of frequent and careful medical management during pregnancy in the patient who has seizures. In case 2 the patient was not seen until the fourth month and had had a good many attacks; thereafter, with careful management, including two hospitalizations and

the use of ion exchange resins to combat sodium and water retention, the patient had only two seizures during the rest of pregnancy. In case 3, seizures occurred on two occasions in association with sudden spurts of weight gain, but these were controlled quickly by the use of Diamox. The effectiveness of this agent is further demonstrated by total body water studies showing a marked fall in total body water. This case illustrates that even a patient with a well controlled seizure state and under careful medical management may still have some increase in attacks during pregnancy.

Case 4 is presented because it represents a patient who probably never would have married except for present day anticonvulsant medication and careful medical management. These brought her from a state of almost complete isolation to a state of normality and resulted in her marriage, following which she became pregnant. This case also demonstrated the severity of seizures in a patient previously controlled for 18 months and now once again controlled after pregnancy. Her management was not perfect and probably results could have been improved had she been hospitalized once or twice.

Case 5 is presented to show the effects of eclampsia in producing a continuing seizure state. This patient eventually had a temporal lobectomy which demonstrated pathology in the temporal lobe. We have had one other similar case who has also had a temporal lobe operation as a result of a seizure state following eclampsia.

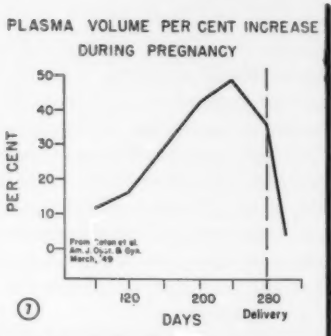
Case 6 is presented to demonstrate the effectiveness of good medical management and restricted weight gain in controlling seizures during pregnancy.

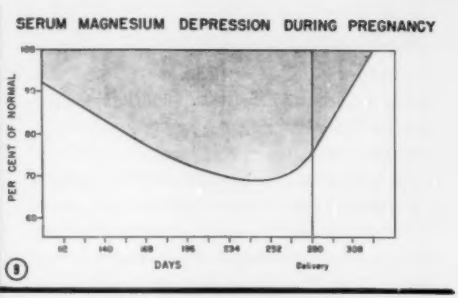
PHYSIOLOGIC CHANGES IN NORMAL PREGNANCY

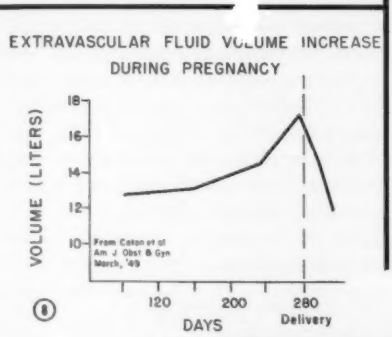
A review of the physiologic changes occurring during normal pregnancy reveals a number of changes, each of which alone has been observed to cause an increase of seizures in susceptible persons. Since these occur in pregnancy, it is understandable why even normal pregnancy should cause an increase in frequency and severity of seizures. The most important of these changes include retention of water, retention of sodium, hyperventilation-compensated alkalosis, increased metabolism, hormone changes, dilution of blood with anemia, and lower magnesium, calcium and sodium levels.

Increased sodium and water retention appears to be a constant accompaniment of pregnancy. Actually few direct studies of total body sodium and total body water have been made during pregnancy and the results leave some doubt concerning both the degree and location of any retention of these substances.[10–12] It is commonly agreed, however, that plasma volume is increased 25 to 50 per cent during pregnancy and interstitial fluid volume increased at least 20 to 25 per cent.[13] The course of these changes during pregnancy is shown in figures 7 and 8.

That retention of fluid by the body does predispose to seizures is a well observed fact and formed the basis of the hydration test which formerly was performed by administering water and Pitressin as an aid to diagnosis in patients suspected of having seizure states. Determination of total body water done by the antipymine method[14,15] in cases 2 and 3 presented above showed that total body water was increased during pregnancy and that peaks of elevation coincided with increased seizures (figures 5







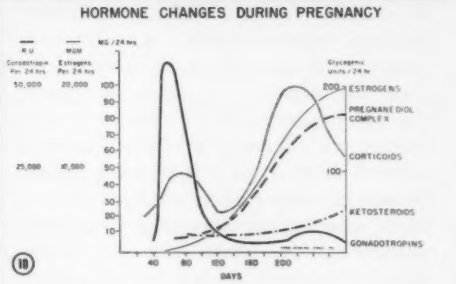


FIG. 7. Increase of plasma volume during pregnancy.
FIG. 8. Increase of extravascular fluid volume during pregnancy.
FIG. 9. Decrease of serum magnesium levels during pregnancy.
FIG. 10. Endocrine changes during pregnancy.

and 6). From these studies it would appear that retention of water and perhaps also of sodium is the most important factor in predisposing the pregnant woman to increased seizures.

Hyperventilation is used routinely to bring out abnormalities in the electroencephalogram and at times precipitates clinical seizures. Increased hyperventilation is a constant finding in pregnancy, apparently being due to an actual increased sensitivity of the respiratory centers.[16] This tendency to hyperventilation is so constant that a mild "acidosis" is produced during pregnancy as a compensation. Fluctuations in this compensation must occur, however, and this may well be a factor in increasing seizures.

We have reported previously on the tendency of magnesium deficiency to produce seizures both in animals and man. During the past year a study of the serum magnesium levels carried out in our laboratory[17] shows that serum magnesium is lowered during pregnancy, this apparently being simply a result of the usual blood dilution mentioned above (figure 9). Though we doubt that this change alone would produce seizures very often, even in a susceptible individual, it is one more factor tending

in that direction. Similar lowering by dilution takes place in serum calcium, hemoglobin, and sodium, and in each case the direction of change is once again that which would produce a lowered seizure threshold.

It is one of the paradoxes of pregnancy (which may or may not be true) that serum sodium is usually lowered during pregnancy, although total sodium retained by the body is increased. This is assumed to cause a change of ratio between intracellular and extracellular sodium, with intracellular sodium being relatively increased. In other situations a similar change has been shown to result in the lowering of seizure threshold.[18] Though studies concerning other tissues have been made, we know of no study which gives a final answer to the relative levels of intracellular and extracellular sodium in the brain during pregnancy.

The increased metabolism, as well as a significant degree of nitrogen retention which occurs during pregnancy, duplicate, at least to some degree, the changes taking place in the body during periods of rapid growth. Such periods of growth are known to predispose to recurrence and increased severity in seizure states, though no explanation for this tendency is available.

Pregnancy is associated with great changes in endocrine balance.[19,20] These changes are almost certainly the real basis of the more readily observed alterations discussed above and, in addition, may well have a direct effect on seizure threshold. A complete discussion of these endocrine changes is impossible, but figure 10 outlines the main events. One recent addition to our knowledge of adrenal corticoids is the isolation and identification of aldosterone, which produces a sodium-retaining action many times greater than any previously investigated steroid.[21] Studies up to the present time indicate that secretion of aldosterone is increased during pregnancy but varies considerably from person to person.[22] It seems likely that further study will give aldosterone an important, if not essential, position among the factors which cause water and sodium retention with a secondary lowering of seizure threshold.

This discussion of physiologic changes in normal pregnancy which might adversely affect seizure states would not be complete without at least mentioning the possibility that anxiety reactions, constipation, fatigue, changes in dietary habits, and other commonplace accompaniments of pregnancy may at one time or another account for increased frequency and severity of seizures in a susceptible person.

COMPLICATIONS OF PREGNANCY AND SEIZURE STATES

As far as this study is concerned, toxemia of pregnancy appears to be the main cause of severe seizure states beginning during pregnancy. When the pathology of eclampsia is reviewed, the wonder is that this condition is not followed more commonly by seizure states. In many respects the pre-eclamptic state appears to be simply an exaggeration of the sodium and water retaining tendency of normal pregnancy. Whether this is true or whether it is a distinctly different process is not known. Clinically, however, there is no question about the production of severe edema and it is possible to conceive of this condition as a tremendously exaggerated hydration test. Added to this are severe vascular changes with hypertension which must

produce tissue ischemia and which, in fatal cases at least, are nearly always associated with extensive cerebral hemorrhage.[6] It is difficult to believe that some minor hemorrhagic changes at least are not present in any patient who experiences an eclamptic episode even though they recover. While damage to the brain resulting in epileptogenic foci from thrombosis and hemorrhage would seem the most likely explanation of continuing seizures after eclampsia, it is certainly possible that cerebral edema alone might produce brain damage even of a focal nature. Since our cases reviewed above indicate the damage is usually in the temporal lobe, it is possible that this occurs from increased intracranial pressure according to the same mechanisms proposed by Penfield for ischemic injury of the temporal lobe at birth.

A number of other complications which arise during or immediately after pregnancy may affect the nervous system so as to cause seizures.[6] The general tendency to increased clotting may be responsble for either arterial or venous thrombosis in the absence of eclampsia. Though none of our cases showed the typical hemiplegic changes associated with venous thrombosis as described by Stevens,[23] this should be considered in those cases of seizures beginning post partum. Also, though no brain tumors occurred in our series, the possibility of a patient with brain tumor first showing nervous system symptoms during pregnancy should never be overlooked.

Further study is needed in this field because there may be many other cases with seizures beginning a number of years after an eclamptic episode in which the connection between the two has not been apparent. In this study there was one case with attacks beginning five years following eclampsia with no other cause evident. We have knowledge of another case beginning 17 years following severe eclampsia with no intervening cause evident. Since it is known that in some cases posttraumatic seizures may not appear for years, the same situation may occur in some patients who have had eclampsia.

PREVENTION AND TREATMENT

It is evident that the prevention of severe toxemia of pregnancy will also result in the prevention of subsequent seizure states in a number of patients. Careful and constant prenatal care may thus prevent a seizure state in the mother, not to mention the possibility of preventing birth injury and subsequent seizure state in the child. That careful prenatal care can prevent toxemia of pregnancy is evident by the increasing rarity of this condition among patients carefully supervised in an obstetric clinic or in private obstetric practice. The most important aspects of treatment of the patient with a known seizure state who becomes pregnant is outlined below:

TREATMENT

- Advice about pregnancy
- Careful supervision of anticonvulsant medication
- Restriction of weight gain
  - Diet — ion exchange resins
  - Diamox — amphetamine
- Restriction of sodium intake
- Hospitalization if:
  - Too much weight gain
  - Too many seizures
  - Any signs of toxemia

The best results are obtained if advice and information concerning the effects of pregnancy on mother and child can be given the patient before pregnancy occurs. From the studies presented in

this paper, it appears that any woman with a known seizure state, contemplating marriage or pregnancy, should be informed that pregnancy might well result in some increased severity and frequency of seizures, but that with good prenatal care and careful supervision of diet and anticonvulsant drugs, this tendency can be counteracted and that a relatively normal pregnancy and delivery can be experienced without harm to the mother or child. There is certainly no evidence from our study which would permit one to advise a patient with a seizure state that pregnancy might improve or "cure" the condition. The danger of pregnancy to the condition of the mother would seem to be greater than any danger to the child. We have seen a number of patients with daily psychomotor seizures occurring throughout the entire course of pregnancy who have had completely normal children. It would appear that the danger to the child is only that of long periods of anoxia such as might occur during a prolonged grand mal seizure or during status epilepticus.

Advice to patients concerning pregnancy should, of course, take into account possible hereditary factors, but it is not the purpose of this paper to go into a consideration of genetics. It can be said that, in general, seizure states based primarily on hereditary factors are much less frequent than was formerly believed and that, even in the face of a very definite hereditary tendency, the degree of transmission of clinical seizures to the children is not great.[8]

Advice to the patient concerning the effect of pregnancy should result in the patient with seizures notifying the physician responsible for treatment of her seizures as soon as she finds that she is pregnant. In this way, plans can be made for careful supervision and complete information about her condition can be transmitted to the physician supervising her care during pregnancy. This is important, since, as McClure[4] has recently pointed out, many patients with seizures do not bother to tell their obstetrician about their condition or even purposely withhold this information from him.

Management of the patient with a known seizure state during pregnancy consists of strict adherence to the principles outlined below. The patient should be advised from the beginning that a minimum weight gain during the entire course of pregnancy is desirable. Weight gain for the entire pregnancy should be kept to 16 to 18 pounds, with no more than two pounds weight gain in any one month. Sudden spurts of weight gain are more detrimental than a slightly greater over-all weight gain for the entire period of pregnancy, since such spurts usually represent an accumulation of fluid. This is demonstrated in case 3. Such a minimum weight gain can only be maintained by having the patient weigh herself regularly and by careful advice as to low-caloric and low-sodium diet. An increase in weight gain is the first sign of accumulated fluid and possible toxemia and should be treated as such. If any evidence of toxemia, such as edema, albuminuria, or hypertension develops, the patient should be treated very intensively and strictly in an attempt to bring this under control.

Treatment, in addition to diet, can consist of ion exchange resins which may be given in courses of one or two weeks and in doses varying from 15 gm. twice a day to 15 gm. four times a day. These are particularly helpful in patients who

have difficulty in maintaining their diet. In addition to the ion exchange resins, diuretics, either in the form of mercurial diuretics or such preparations as Diamox, can be used.

It has been our experience that, if results cannot be obtained on an outpatient basis, good results usually can be obtained by a week or two of hospitalization and strict supervision of the patient. Such hospitalization may prevent a severe recurrence of seizures and in a relatively short time in the hospital a considerable reduction in weight and fluid retention can be achieved. Cases 2 and 3 have been presented to emphasize this point. It has even been observed that patients with fluid retention often lose two to four pounds during the first day of hospitalization, even before special diets and therapy are instituted.[11]

Equally as necessary is the regulation and adjustment of anticonvulsant medications. The patient should be continued on the drugs which have controlled the seizures in the past, and, if the seizures are not completely controlled, new drugs can be added gradually during pregnancy. In no instance should drugs be withdrawn quickly and if for any reason, such as nausea and vomiting, the patient cannot take the usual medication by mouth, means should be provided either by suppository or by injection to keep her on a regular amount of anticonvulsant medication. This possibility should be anticipated so that the patient will not wait until after it has happened to consult her physician. If necessary, patients can be carried on fairly high doses of injected sodium phenobarbital until oral medication can be resumed. This is true both during pregnancy and during the time of labor and delivery, when patients often miss their oral medications.

CONCLUSIONS

A study of 177 women with seizure states who have also been pregnant reveals that pregnancy often produces an increased frequency and severity of seizures, and that a number of patients have onset of their seizure states during pregnancy. In some cases the onset of a seizure state appears to be a direct result of complications of pregnancy such as eclampsia.

A number of physiologic changes take place during pregnancy which tend to increase frequency of seizures. These include retention of sodium and water, a tendency to hyperventilation, lowering of magnesium, calcium, hemoglobin, and sodium levels in the blood by dilution, and hormone changes, including increased production of sodium-retaining adrenal corticoids.

Treatment of patients with seizure states who become pregnant should include advice concerning the need for careful medical management during pregnancy, necessary measures to limit weight gain and sodium and water retention, measures to assure regular and continuous medication, and hospitalization for control of weight or seizures if necessary.

Cases are reported which demonstrate the effect of pregnancy on seizure states and show the effectiveness of the use of ion exchange resins, diuretics, strict diet, and hospitalization in treatment.

It is concluded that pregnancy should be approached with caution in women with seizure states, but that with careful management, a relatively normal pregnancy and delivery can occur without harm to the mother or the child.

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■ Epilepsy has been distinguished by a great variety of names, such as *morbus sacer, comitialis, Herculeus, caducus,* &c. Aretaeus says, it may have been called sacred on account of the magnitude of the evil, it being customary to call what is great by that name; or because it is to be cured rather by divine than by human power, or because persons labouring under it have been thought possessed by demons. Hippocrates, although he has described the disease under the title sacred, ridicules the opinion that it has any connexion with supernatural influence. The complaint called sacred, he says, appears to be in no respect more divine than others, having, like them, its own particular nature and origin. He maintains that he can point out many disorders not less wonderful in their symptoms, to which no one ever thought of applying the term sacred. Besides, he remarks, if we attribute the disease to the gods, we ought to seek its cure in the temples.

John Cooke in *A Treatise on Nervous Diseases,* published in 1824.

Effect of Diamox on Cerebrospinal Fluid Pressure of Cat and Monkey

Lawrence M. Knopp, M.D., James R. Atkinson and Arthur A. Ward, Jr., M.D.*

DIAMOX (2-acetylamino-1,3,4-thiadiazole-5-sulfonamide acetozoleamide) is a potent carbonic anhydrase inhibitor which appears to decrease the rate of formation of cerebrospinal fluid[1] and of intraocular fluid,[2–4] resulting in a decrease in pressure in each system. The role of Diamox in carbonic anhydrase inhibition has been well documented,[5] but the role of carbonic anhydrase in the circulation of cerebrospinal fluid and intraocular fluid is incompletely understood.

Tschirgi and co-workers[1] studied the effect of intravenous Diamox on cerebrospinal fluid formation in cats and rabbits. The reported decrease in cerebrospinal fluid formation and pressure suggested the use of Diamox in selected patients with increased intracranial pressure. Prior to clinical trial, some of the pertinent additional studies included the effect of Diamox on cerebrospinal fluid pressure of: 1) cats, repeating the earlier studies, 2) lower primates, whose cerebrospinal fluid systems are physiologically nearer to that of man, and (3) lower primates with increased intracranial pressure. Accordingly, the present study included three groups of animals: 1) cats with normal cerebrospinal fluid pressure, 2) monkeys with normal cerebrospinal fluid pressure, and 3) monkeys with elevated cerebrospinal fluid pressure.

MATERIALS AND METHODS

Thirteen adult cats, two adult monkeys (Macacus rhesus), and three immature monkeys (Macacus radiata) were used. Intraperitoneal sodium pentobarbitol, 35 mg./kg., was used for anesthesia. With the animal in the lateral decubitus position, a cisternal puncture was made with a No. 18 one and one-eighth-inch spinal needle which was connected to the pressure recorder through a three inch length of saline-filled polyethylene tubing with an inside diameter of 0.062 inch. Two types of pressure recording systems were used; one was a resistance wire strain gauge operating through a balance demodulator amplifier system to a pen writer; the other type was a directly coupled saline-filled manometer with a bore of 2 mm. Ar-

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terial and venous pressures were recorded with direct reading manometers. Respirations were monitored visually. One cc. of intravenous 5 per cent sodium polyanhydromanuronic acid sulfate (Paritol) was used as an anticoagulant. Following a minimum 30 minute control period, 150 mg./kg. intravenous Diamox (100 mg./cc.) was injected rapidly. Cerebrospinal fluid, arterial, and venous pressures and respirations were then monitored.

Increased intracranial pressure was produced in the two adult monkeys by the subdural implantation of psyllium seed. Through a three-fourths inch right frontal trephine opening, a slit was made in the dura and 2¼ cc. of dry psyllium seed was introduced by sliding the seed along the surface of a small brain spoon. A water-tight dural closure was made, the bone button wired in place and sealed with bone wax, and a two-layered scalp closure performed. The seed was so markedly hygroscopic that rapid dural closure was necessary to prevent bulging of the artificial tumor mass through the dural incision during the short surgical procedure. This amount of psyllium seed produced a markedly increased intracranial pressure within 30 minutes. At post mortem, each animal had a psyllium seed tumor of approximately 20 cc. mass.

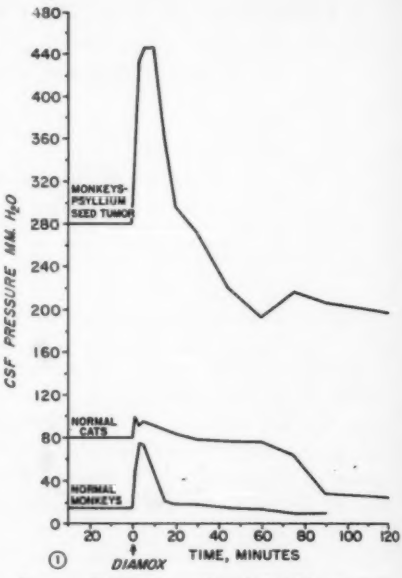

FIG. 1. Changes in cerebrospinal fluid pressure after intravenous Diamox (150 mg./kg.).

RESULTS

Following Diamox injection, there was an immediate increase in cerebrospinal fluid pressure in normal cats, normal monkeys, and monkeys with space-occupying lesions, with a return to initial levels within 30 minutes (figure 1). The time course of cerebrospinal fluid changes did not coincide with changes in arterial and venous pressure (figures 2 and 3). Apnea was present in some animals in each group. When present, it occurred immediately following Diamox injection and persisted for periods up to one minute.

Normal cats. The cerebrospinal fluid pressure of normal cats rose to an average high value 25 per cent above the initial level within one minute following Diamox administration and returned to the initial level within 30 minutes. The cerebrospinal fluid pressure fell slowly thereafter and by the end of 90 minutes after injection of Diamox it was less than 50 per cent of the initial value. Both arterial and venous pressures showed a transient increase following Diamox administration, tending to return to their initial pressures more rapidly than did cerebrospinal fluid pressure (figure 2). Three cats had a one minute period of

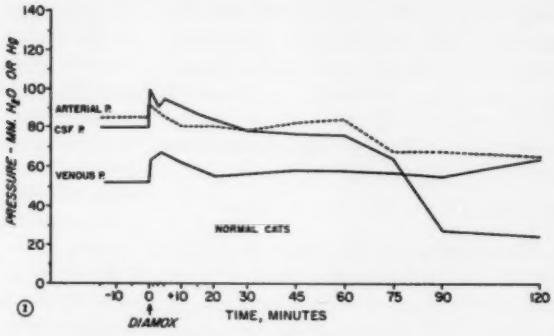

FIG. 2. Relation of cerebrospinal fluid pressure to arterial and venous pressures after intravenous Diamox (150 mg./kg.) in cats.

apnea immediately after the injection of Diamox, following which normal respirations recurred. The remaining cats had no change in respiratory pattern throughout the procedure.

Normal monkeys. There was a fourfold increase in cerebrospinal fluid pressure in these animals which reached its peak within three minutes after Diamox injection, returning to near its initial value within 15 minutes (figure 1). Little further change in cerebrospinal fluid pressure was observed up to 90 minutes after Diamox administration, and the late drop in cerebrospinal fluid pressure seen in the cat experiments was not observed. Arterial and venous pressures were not followed in these animals. Each showed a 45 second period of apnea, followed by one to two minutes of diminished respiration before a return to a normal respiratory pattern.

Monkeys with space-occupying lesions. The initial cerebrospinal fluid pressure of these monkeys with psyllium seed tumors averaged 280 mm. of water 30 minutes after operation. (The individual initial pressures were 265 mm. and 295 mm., respectively.) Following Diamox administration, the cerebrospinal fluid pressure rose precipitously to an average high of 450 mm. at ten minutes. Since one of these two animals developed its highest pressure (538 mm.) at three minutes and the other (480 mm.) at ten minutes, the average figure quoted above gives an erroneously low peak value. By the end of 30 minutes after injection of Diamox, the cerebrospinal fluid pressure had returned to normal. There was a subsequent slow fall to a low value 38 per cent below the initial cerebrospinal fluid pressure within 60 minutes after Diamox administration (figure 1). There were no abrupt changes in arterial or venous pressure following Diamox (figure 3). One animal had a normal

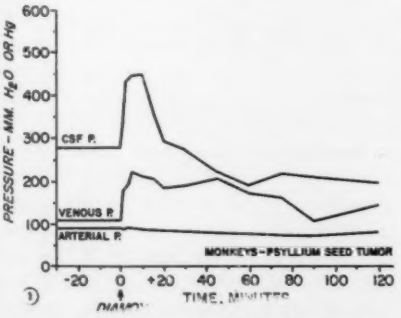

FIG. 3. Relation of cerebrospinal fluid pressure to arterial and venous pressures after Diamox (150 mg./kg.) in monkeys with psyllium seed tumor.

respiratory pattern throughout the experiment. The other monkey had marked respiratory depression during the period of maximum increased cerebrospinal fluid pressure, returning to a normal respiratory pattern as intracranial pressure dropped to near baseline levels.

DISCUSSION

The purpose of this series of experiments was to observe the effects of large intravenous doses of Diamox on the cerebrospinal fluid pressure of cats and monkeys. The drug produced an acute increase in intracranial pressure in all the animals tested. In normal cats and in monkeys with increased intracranial pressure, there was an ultimate fall in cerebrospinal fluid pressure below the initial level. In contrast, there was no fall in cerebrospinal fluid pressure in normal monkeys at any time. Slightly less than half the animals had an initial period of respiratory embarrassment.

Two factors can be shown to play no consistent role in the observed pressure changes. The control injection of a volume of saline equal to the Diamox injection mass produced no changes in cerebrospinal fluid pressure. Likewise, there were no significant pressure alterations during control periods under anesthesia of up to two and a half hours. It thus appears reasonable to assume that the pressure changes were due to the administration of the drug.

Our results are at variance with those reported by Tschirgi and co-workers.[1] It is difficult to explain the fact that they observed no acute rise in intracranial pressure. Their animals were paralyzed and artificially respirated, while ours were not. The curves with which they illustrate the effect of increased carbon dioxide concentrations on cerebrospinal fluid pressure show a striking similarity to the changes we observed following Diamox administration, although the time course was not identical. It seems unlikely that artificial control of respiration could play any great role in suppressing the acute changes we observed, since the greater number of our animals had no alterations in respiratory rate or rhythm.

An acute increase in intracranial pressure can be produced only by an acute increase in intracranial mass. This may be achieved only by an increase in the volume of cerebrospinal fluid, brain tissue, or intracranial vascular components. The present study has produced no evidence pointing specifically to any one of these factors, yet the observed changes, when viewed in the light of the known actions of Diamox permit some reasonable speculations.

It is known that changes in carbon dioxide tension produce alterations in the volume of the intracranial vascular compartment. The vascular dilatation accompanying elevated carbon dioxide tension results in elevated cerebrospinal fluid pressure. This mechanism could be responsible for the rise in cerebrospinal fluid pressure in those animals which experienced respiratory embarrassment, but elevated carbon dioxide secondary to apnea will in no way account for the pressure changes in the remaining animals of the series.

Nevertheless, changes in plasma carbon dioxide which are independent of respiration could account for the acute transitory changes in intracranial pressure noted in all the animals of this series. The administration of Diamox results in an increase in plasma carbon dioxide and hence, presumably, in cerebral carbon dioxide. This can result in

intracranial vascular dilatation with resultant increase in intracranial pressure. Hence, a mechanism exists which is capable of producing changes in intracranial vascular volume without accompanying respiratory alterations.

Despite the fact that the ultimate effect of Diamox administration may be that of a delayed decrease in cerebrospinal fluid pressure, the acute increase in pressure observed after administration of large intravenous doses suggests that clinical trial is not yet advisable as a means of reducing intracranial pressure. In particular, the rather massive increase in intracranial pressure noted in those animals with space-occupying lesions is capable of producing grave alterations of central nervous system function, as indeed it did in the monkey who developed Cheyne-Stokes respiration during the period of maximum increased cerebrospinal fluid pressure following Diamox. Thus, the administration of such large intravenous doses of Diamox in patients with elevated cerebrospinal fluid pressure, and especially those with a mass lesion, could conceivably result in an increase in intracranial pressure of lethal proportions.

SUMMARY

1. Intravenous Diamox in doses of 150 mg./kg. produced an immediate increase in cerebrospinal fluid pressure in cats and monkeys from 25 to 400 per cent above the initial level. Normal cerebrospinal pressure levels were regained within 30 minutes. The ultimate cerebrospinal fluid pressure was 25 per cent to 60 per cent below the initial level in normal cats and in monkeys with increased intracranial pressure, but not in normal monkeys.

2. Elevated cerebrospinal fluid pressure was produced in two monkeys by the subdural implantation of psyllium seed. Elevations of pressure after Diamox administration in these animals reached potentially lethal levels.

3. It is postulated tentatively that the increase in cerebrospinal fluid pressure is due to increased volume of intracranial vascular structures, secondary to elevated cerebral carbon dioxide resulting from carbonic anhydrase inhibition by Diamox.

4. Clinical trial of Diamox in this dosage for treatment of increased intracranial pressure is not advised.

Diamox supplied by Lederle Laboratories.

We wish to acknowledge the assistance of Mr. Elmer Mullin during the course of these experiments.

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Collateral Regeneration from Residual Motor Nerve Fibers in Amyotrophic Lateral Sclerosis

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In 1945 American investigators found experimental partial muscle denervation to be followed by a rapid and considerable improvement of the muscle strength.[1–3] It has since been shown that the improvement is due to collateral sprouting from surviving nerve fibers, the sprouts re-innervating denervated muscle fibers to a considerable extent.[4–7] Wohlfart and Hoffman[8] showed that collateral sprouting plays an important role in the regression of the palsies in experimental mouse poliomyelitis.

Evidence is now available that collateral sprouting can also occur in human beings.[9–12] Wohlfart[9] pointed out that collateral sprouting is found in amyotrophic lateral sclerosis and in human poliomyelitis. Coers[10] reported collateral sprouting in human poliomyelitis, Werdnig-Hoffman's disease, polyneuritis and amyotrophic lateral sclerosis, and Woolf[11] and Woolf and Till[12] in spinal root compression.

This paper is concerned with collateral sprouting in amyotrophic lateral sclerosis and its bearing on some clinical problems.

MATERIAL AND METHODS

The material consisted of muscles and nerves removed at autopsy from six patients with amyotrophic lateral sclerosis. In all of these cases the clinical picture had been typical and the postmortem findings in the spinal cord were classic.

Intramuscular nerves were demonstrated in frozen muscle sections impregnated according to Gros-Schultze's silver method. In some cases thin slices of muscle fixed in formol were osmicated for myelin of intramuscular nerve trunks. Peripheral nerves were fixed in formol and either stained with osmium tetroxide or paraffin sections were stained according to Davenport's silver method.

Frozen sections were stained with methyl violet for amyloid corpuscles. The metachromasia of the intramuscular nerve trunks was demonstrated with toluidine blue. In addition, ordinary stains such as hematoxylin-eosin and iron hematoxylin-van Gieson were used throughout.

In some other clinically verified cases of amyotrophic lateral sclerosis, biopsy specimens were impregnated in accord-

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Preliminary results of the present investigation were presented at the German Neurological Congress in Würzburg and at the Swedish Poliomyelitis Conference (1954).

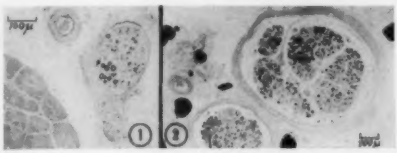


FIG. 1. Man, aged 61. Amyotrophic lateral sclerosis. Autopsy. Anterior tibial muscle. Osmium tetroxide stain. A large intramuscular nerve trunk showing a pronounced loss of myelinated nerve fibers. Despite this, most muscle fibers were of normal size and relatively few groups of atrophic fibers were found.

FIG. 2. Man, aged 52. Amyotrophic lateral sclerosis. Autopsy. Transverse section through the most proximal part of the nerve of the medial head of the gastrocnemius. Osmium tetroxide stain. Extreme loss of myelinated motor fibers, most of the remaining ones being afferent. In spite of this, all parts of the corresponding muscle contained many normal-sized and innervated fibers.

ance with Löwit's gold method for intramuscular nerve fibers.

RESULTS

The present study was prompted by the postmortem observation in a case of amyotrophic lateral sclerosis of a considerably reduced number of large nerve fibers, even in muscles showing no groups of wasted muscle fibers. Systematic study of the tissue specimens removed at the six autopsies revealed that the number of large nerve fibers of the intramuscular nerve trunks is regularly more reduced in amyotrophic lateral sclerosis than what might be expected from the degree of wasting. Figure 1 shows an example of extreme loss of large nerve fibers, though the disseminated neurogenic muscular atrophy was only moderate.

Similar findings were made in the main muscle nerves. An example of extreme loss in the nerve of the medial head of the gastrocnemius is shown in figure 2. In spite of this, all parts of the corresponding muscle contained many innervated muscle fibers.

In another instance, a seemingly normal medial head of the gastrocnemius was found to be supplied by a nerve in which one-fourth to one-fifth of the total number of nerve fibers had been destroyed. Clinically that muscle had shown fasciculations but no definite weakness or wasting. On microscopic examination this muscle contained only a few groups of atrophic muscle fibers, the main bulk of fibers being innervated.

The observations described above suggested that, in amyotrophic lateral sclerosis, surviving large nerve fibers might branch and re-innervate denervated muscle fibers.

In all of the six cases studied, silver impregnation revealed that the intramuscular nerve trunks contained numerous thin nerve fibers varying in diameter down to scarcely visible ones in the light microscope (figure 3). Knobs were often seen in the course of these thin fibers (figures 3 and 5). There can be no doubt that the number of thin fibers is much increased in the intramuscular nerve trunks in amyotrophic lateral sclerosis. The large fibers are, on the other hand, more or less reduced in number.

Knobs of the type shown in figures 3 and 5, for example, are not seen in muscle specimens from normal young adults, but are occasionally demonstrable in specimens from elderly persons. Such thickenings have been described by Tello[13] and Cajal[14] in regenerating fibers of intramuscular nerve trunks following section of the corresponding nerve. Tello pointed out that triangular thickenings of the type shown in figures 5 and 8 are typical of regenerating fibers at bifurcations. In all cases of amyotrophic lateral sclerosis in this material, knobs were common, both in

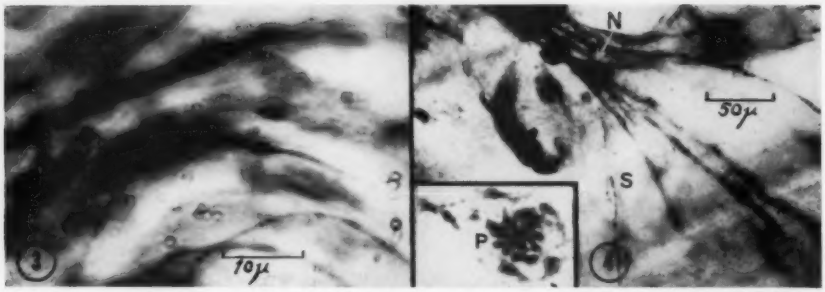


FIG. 3. Man, aged 76. Amyotrophic lateral sclerosis. Autopsy. Part of intramuscular nerve trunk from the medial head of gastrocnemius. Gros-Schultze silver method. The figure shows one normal fiber and several thin regenerating fibers with knobs in their course.

FIG. 4. Woman, aged 65. Amyotrophic lateral sclerosis. Biopsy from vastus medialis. Löwit gold method. The figure shows a group of terminal motor nerve fibers with a thin collateral sprout at *S*. It extends from the node *N* of a normal fiber. A normal end-plate from the same preparation has been inserted in the lower left corner.

thin and thick fibers (figures 6, 8, and 9).

Normally, thin fibers are seen in the larger intramuscular nerve trunks, but the terminal motor bundles are made up of thick fibers only. In amyotrophic lateral sclerosis, it is often observed that the terminal fibers differ from one another in caliber. A normal terminal fiber and a thin fiber, obviously a regenerating one, both running in neurilemma sheaths are seen in figure 7. The endings are not seen at this focusing level. The appearance of the terminal nerve fibers in a gold-impregnated muscle biopsy specimen in fairly early amyotrophic lateral sclerosis is shown in figure 4, from which it is apparent that a sprout (S) is given off from a node (N) of a normal fiber.

Attention was then directed to the endings of the nerve fibers. Figure 10 shows normal end-plates in amyotrophic lateral sclerosis, as demonstrated by the Gros-Schultze technic on autopsy material. The end-plates, as shown by this technic, appear as simple bifurcations of the terminal nerve fiber surrounded by nuclei. Only occasionally a few finer

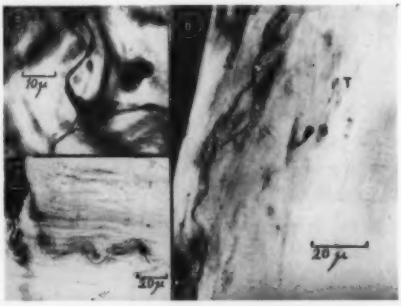


FIG. 5. Man, aged 76. Amyotrophic lateral sclerosis. Autopsy. Gros-Schultze method. Detail from an intramuscular nerve trunk in the medial head of gastrocnemius. The triangular swelling of the bifurcating fiber is a sign of regeneration. The "daughter fibers" run in widely different directions.

FIG. 6. Man aged 76. Amyotrophic lateral sclerosis. Autopsy. Gros-Schultze silver method. The figure shows a collateral sprout from a surviving normal nerve fiber in an intramuscular nerve trunk. The collateral leaves the trunk and, after the formation of several knobs along its course, it ends in the connective tissue. From the large knob at *B*, there extends a thin fiber ending in a terminal thickening at *T*.

FIG. 7. Man, aged 76. Amyotrophic lateral sclerosis. Autopsy. Medial head of gastrocnemius. Gros-Schultze silver method. Terminal portion of one normal fiber and one regenerating fiber, both running within neurilemmal sheaths. The endings are not seen at this focusing level.

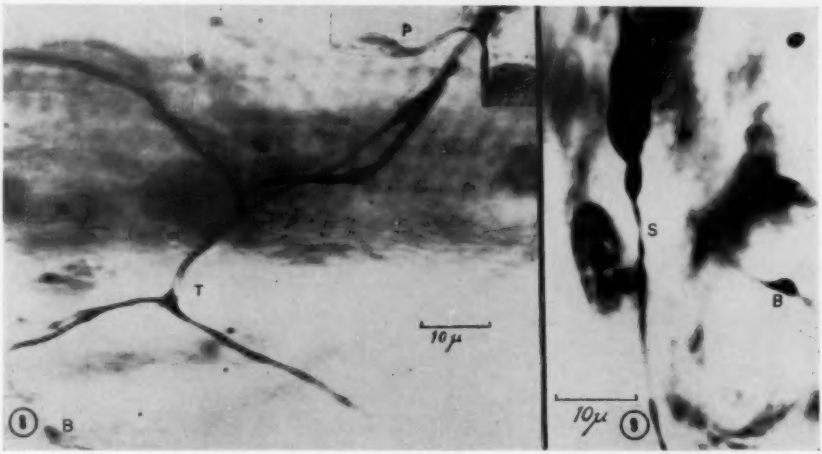


FIG. 8. Man, aged 76. Amyotrophic lateral sclerosis. Autopsy. Gros-Schultze silver method. Terminal part of a group of regenerating motor nerve fibers in the medial head of gastrocnemius. At *P* an end-plate of normal type is seen. *T* indicates the typical triangular swelling of regenerating fibers at bifurcations. *B* shows a typical terminal ball (growth cone). Note also the thin branches growing in different directions and seen at *T*, for example.

FIG. 9. Man, aged 76. Amyotrophic lateral sclerosis. Autopsy. Medial head of gastrocnemius. Gros-Schultze silver method. At *S* a thin regenerating fiber ending with a growth cone of peculiar type is seen. At *B* part of another thin regenerating fiber is observed.

branches are seen. A normal end-plate (P), as seen in gold-impregnated muscle biopsies, has been inserted in figure 4. An end-plate innervated by a thin regenerating fiber is discernible in figure 12. It was often noticed that a single terminal motor nerve fiber extended to several end-plates. Normally such fibers do not innervate more than one or two end-plates.

In amyotrophic lateral sclerosis, the end-plates are sometimes changed in a conspicuous way: instead of a simple bifurcation, one sees extensive arborization covering a large area of the muscle fiber. These elaborate endings often give off ultraterminal branches forming end-plates on other muscle fibers. The ultraterminals are best seen in gold preparations. Empty Schwann sheaths, the end result of the degenerative process, were seen frequently, of course.

Many nerve fibers are obviously outgrowing, but have not yet reached any connection with muscle fibers. Such fibers end with the typical knobs and often also show knobs in their course. Figure 6 illustrates this. To the left in the figure, one can see a small intramuscular nerve trunk containing only one surviving large nerve fiber. A collateral sprout, originating in the large fiber, is leaving the trunk and ends after several thickenings in the connective tissue. Figure 8 is also elucidating. A group of terminal motor fibers are branching several times. One of the branches is connected with an end-plate (P). Another branch is still growing and ends with a typical terminal ball (B). Figure 9 shows a

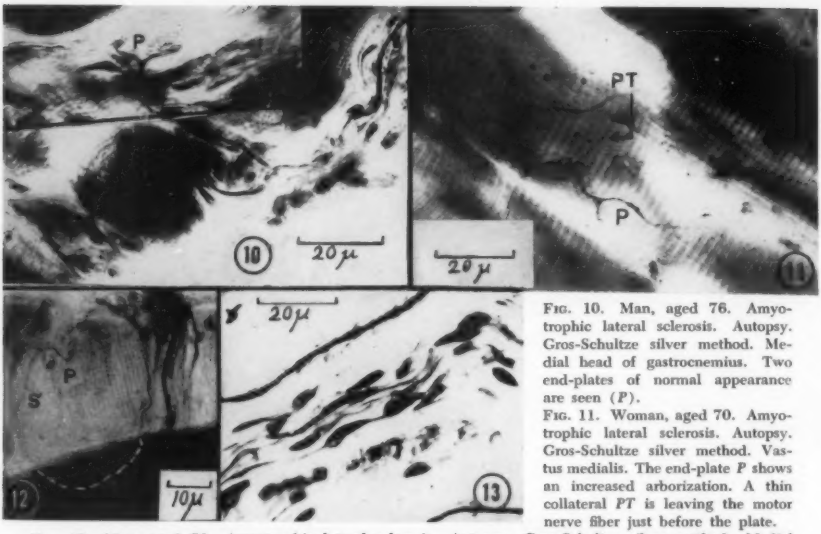


FIG. 10. Man, aged 76. Amyotrophic lateral sclerosis. Autopsy. Gros-Schultze silver method. Medial head of gastrocnemius. Two end-plates of normal appearance are seen (*P*).

FIG. 11. Woman, aged 70. Amyotrophic lateral sclerosis. Autopsy. Gros-Schultze silver method. Vastus medialis. The end-plate *P* shows an increased arborization. A thin collateral *PT* is leaving the motor nerve fiber just before the plate.

FIG. 12. Man, aged 76. Amyotrophic lateral sclerosis. Autopsy. Gros-Schultze silver method. Medial head of gastrocnemius. The figure shows a thin sprout S running to an end-plate *P* of normal type. Compare the diameter of the sprout and that of the normal fiber.

FIG. 13. Man, aged 64. Amyotrophic lateral sclerosis. Autopsy. Detail from the sciatic nerve. Davenport silver method. One degenerating and two normal nerve fibers are seen. In the center of the micrograph is a bundle of tiny collaterals.

thin sprout ending with a growth cone of peculiar type. (See also figure 16 *a*.) Figure 14 demonstrates a very thin collateral sprout (S) having its origin in a knob of a normal fiber.

The knobs of the fibers of the intramuscular nerve trunks often assume considerable proportions. Some of these large knobs undergo degeneration, with central loss of their argentophilic property (figure 15). Staining with methyl violet indicates that they are being transformed into amyloid corpuscles. This has also been shown for certain amyloid bodies in the central nervous system. In amyotrophic lateral sclerosis, amyloid bodies connected with nerve fibers in the intramuscular nerve trunks are often numerous (figure 15). Intramuscular nerve trunks normally show slight metachromasia when stained with toluidine blue. In amyotrophic lateral sclerosis, staining is usually more intense.

In only one case of amyotrophic lateral sclerosis were extramuscular parts of peripheral nerves studied with silver methods. The number of large fibers was found to be reduced to a varying extent and degenerating fibers were common. The number of thin fibers was strikingly increased. Figure 13 shows a group of tiny fibers following a Buengner band.

COMMENT

The general principles of collateral sprouting in animals are now fairly well known from the experimental work of Hoffman,[4,16] Edds,[5,17] Edds and Small,[18] van Harreveld,[6] and Causey and Hoffman.[19]

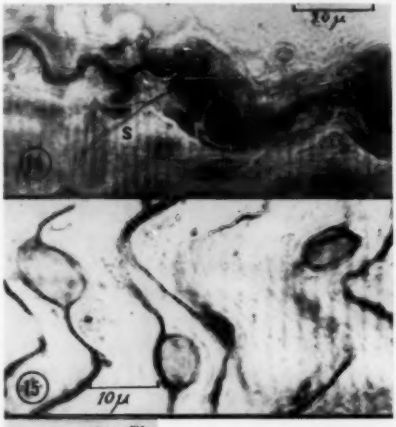
If a degenerating nerve fiber is situated close to a normal nerve fiber, the latter will give off numerous collateral sprouts along its entire course. This sprouting is probably induced by the release of some substance from the degenerating fiber. The new-formed branches enter the Buengner bands formed by the Schwann cells. Causey and Hoffman[19] and Wohlfart and Hoffman[8] demonstrated that several branches enter each Buengner band. Sprouting starts early, probably within the first 24 hours of nerve fiber degeneration.

The Buengner bands form paths, along which the thin sprouts grow to the motor end-plates. The out-growing fibers are characterized microscopically by a terminal knob or ring. The outgrowth is rapid and the denervated end-plates are usually re-innervated within a week or two. Re-innervation is ascribable mainly to sprouts formed from intramuscular portions of the surviving nerve fibers.

The sprouts are thin at first and lack Ranvier nodes. Following partial denervation by surgical methods, they mature rapidly and assume the appearance of normal nerve fibers. As pointed out especially by Edds,[5] the normal terminal innervation ratio, that is, the ratio between the number of end-plates and the number of fibers in the terminal nerve fiber bundle, is only slightly more than 1:1. Following re-innervation in mouse poliomyelitis, this ratio can be as much as 5:1.[8]

A special kind of sprouts are those given off by end-plates and re-innervating adjacent plates. Such "ultraterminals" are common in the rat but rare in the mouse.

Causey and Hoffman had the impression that only few of the collateral sprouts from the peripheral nerves outside the muscles ever mature. Occasionally such sprouts might, however, reach end-plates. Wohlfart and Hoffman found double innervation of a few end-plates in mouse poliomyelitis, a finding probably indicating that two different sprouts have reached the same end-plate. In peripheral nerve lesions, an end-plate re-innervated by a collat-



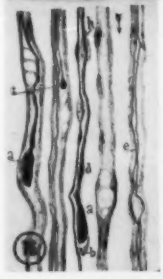


FIG. 14. Woman, aged 70. Amyotrophic lateral sclerosis. Autopsy. Gros-Schultze silver method. Vastus medialis. Collateral sprout S extending from a knob in a nerve fiber of normal diameter.

FIG. 15. Woman, aged 70. Amyotrophic lateral sclerosis. Autopsy. Gros-Schultze silver method. Lateral head of gastrocnemius. Three knobs are being transformed into amyloid corpuscles.

FIG. 16. Sheaths of the peripheral stump of a nerve 78 days after the section: *a*, large clubs of growth oriented toward the periphery; *b*, diverticulum of the sheath which surrounds the club; *d*, preterminal dilatation of the latter; *c*, fine club; *h*, nuclei of two fibers which are situated interstitially; *e*, very fine fibers; the arrow shows the direction of growth. (From Ramon y Cajal: Degeneration and Regeneration of the Nervous System, p. 232.[14])

eral sprout might also receive the originally interrupted axon. End-plates receiving two nerve fibers ("hyperneurotized plates") do not seem to occur normally.

The present investigation as well as the works of Coers,[10] Woolf,[11] and Woolf and Till[12] suggests that collateral sprouting may play the same role in human beings as in the experimental animals studied by earlier investigators.

Since most of the present material was obtained at autopsy, it was necessary to use the silver technic for nerve fiber studies. This technic gave good results, but the resulting slides differed somewhat from those obtained by gold impregnation usually employed in animal studies. Nevertheless, the accompanying illustrations show many examples of intramuscular nerve trunks with thin fibers, which must be newly formed. Figures 6 and 14 show typical instances of thin sprouts given off by normal fibers. Figures 8 and 9 illustrate typical terminal knobs at the end of out-growing fibers.

In the present cases of amyotrophic lateral sclerosis, knobs were demonstrated along the course of fibers in practically all partially denervated intramuscular nerve trunks. Such knobs have not been described earlier in collateral sprouting. These formations are discussed below.

From the classic studies of nerve regeneration by Cajal[14] and his contemporaries, who mainly used pyridine silver methods, it is known that out-growing regenerating fibers, both in the peripheral and the central nervous system, terminate in a knob (figure 16). Such knobs are also seen at the end of fibers in embryonic life and are sometimes referred to as "growth cones."

Tello[13] showed that, some months after division of the sciatic nerve, the intramuscular nerve trunks of previously denervated muscles contain both thicker and fairly thin nerve fibers, with numerous knobs along their course and one at the terminal tip. Tello's illustrations of this regeneration are strikingly similar to those seen in amyotrophic lateral sclerosis.

The knobs undoubtedly contain some substance with latent growth properties. Thin branches are often seen radiating in different directions from these knobs (figures 8 and 14). Such large knobs as are seen at *B* in figure 6 and in figure 14 are certainly caused by some obstacle in the path of the out-growing fiber. An analysis of the submicroscopic structure of these knobs would be of great interest.

As mentioned above, some of these knobs degenerate into amyloid corpuscles. A similar mode of development of certain amyloid bodies in the central nervous system was described by Catola and Achucarro.[15] The regenerative changes described were naturally accompanying degeneration of many nerve fibers. Toluidine blue staining often showed that the intramuscular nerve trunks in amyotrophic lateral sclerosis were definitely more metachromatic than normal trunks. A diffuse metachromasia is known to occur in growing tissues.[20] Holmgren and Rexed[21] demonstrated that the proliferating Schwann cells of Buengner bands show metachromasia. The metachromasia in amyotrophic lateral sclerosis is probably of the same nature.

In amyotrophic lateral sclerosis typical thin regenerating fibers were often seen extending to end-plates (figure 12). In gold-impregnated biopsy specimens, one often observed the typical picture

of a thin sprout in a neurilemma sheath and running to an end-plate.

Ultraterminal out-growth, first demonstrated in human material by Coers[10] by the methylene blue technic in biopsy specimens, seems to be common. Typical of such end-plates in the present investigation was that, on silver impregnation, they showed an increased ramification of the terminal branches, one of them running from the end-plate to an end-plate in another fiber.

In amyotrophic lateral sclerosis, the peripheral nerves generally show a striking reduction in the number of large nerve fibers in relation to the degree of muscular atrophy. In one case in which several large peripheral nerves were impregnated with silver, these were filled with groups of thin nerve fibers following the Buengner bands (figure 13).

It must be assumed that these thin fibers are the result of collateral sprouting at proximal levels. It is not known whether or not some of these fibers join any muscle fibers. It is possible that investigation by physiologic methods might elucidate this problem.

Summarizing, it can be concluded that collateral sprouting plays an important role in amyotrophic lateral sclerosis. Every time a ventral horn cell is destroyed, the gap in the muscular innervation probably is rapidly filled by collateral sprouts from adjacent motor units. In the early stage of the disease most of the muscle fibers are re-innervated in time to prevent any appreciable muscle wasting.

The more scattered the degenerating nerve cells, the better are the conditions for collateral sprouting. The quantitative studies mentioned above show that at least one-third of the motor nerve fibers in amyotrophic lateral sclerosis may be destroyed before the muscle shows any clinical signs of atrophy. Later on, the sprouting process is not sufficient to re-innervate the denervated muscle fibers and then more and more bundles of atrophic fibers appear and produce the well known picture of disseminated neurogenic atrophy.[22] For comparison, it should be mentioned that Edds and Small[18] studied the quantitative aspects of sprouting in monkeys. They found that a denervation of 83 to 90 per cent was not followed by any functional improvement and only sporadic collateral sprouting could be found microscopically. On the other hand, a denervation of 50 to 75 per cent was followed by almost complete re-innervation by sprouting.

Sharrard,[23] who studied human poliomyelitis clinically and histopathologically, observed one case in which the ventral spinal roots of the lumbar region were markedly atrophic and the corresponding muscle groups showed no signs of wasting. This observation is in complete agreement with the present findings in amyotrophic lateral sclerosis and can be explained by the general increase in the size of the motor units by sprouting.

As to amyotrophic lateral sclerosis, it may be concluded that weakness or wasting does not appear until months or years after onset of the disease. This is supported by the occurrence of fasciculation of muscles of normal volume and strength. A biopsy specimen from such a muscle in the present investigation (figure 4) showed some sprouting.

An earlier author noticed a "disparity in the disease of the peripheral motor nerves or of the ventral spinal roots, and of the ventral cornual cells, for the latter may be enormously reduced in number

or severely degenerated though the fibres to which they give origin may be in the majority intact or but very little affected."[24] This old observation may be explained by the process of collateral sprouting. As the peripheral nerves are filled with thin fibres in increased number, they may seem relatively little affected when stained with myelin stains. The earlier authors mentioned did not usually use silver stains for peripheral nerves.

It is possible that collateral sprouts are being formed also in the ventral spinal roots, but hitherto this problem has not been studied either in animals or in human material. Collateral sprouting must play an important role in all human diseases with partial denervation of muscles, as well as in partial traumatic nerve injuries.

The regression of the palsies in poliomyelitis has been ascribed mainly to the recovery of affected but surviving nerve cells. The part played by hypertrophy of the surviving muscle fibers has been a matter of controversy. Bowden[25] discussed the possible significance of sprouting in human poliomyelitis, this mechanism being found in monkeys "at least to some extent." It seems possible, however, that sprouting may be of even greater significance than the recovery of the nerve cells.

Sprouting must be an important factor in the delay of weakness and wasting in hereditary disease characterized by progressive degeneration of lower motor neurons, such as Charcot-Marie-Tooth's disease, hereditary proximal spinal muscular atrophy,[26,27] and infantile spinal muscular atrophy (Werdnig-Hoffman's disease). This also applies to syringomyelia, tumors, and other spinal diseases leading to ventral horn destruction. Woolf[11] mentioned that sprouting occurs in muscles in cases of spinal root compression. The present writer is able to confirm this on the basis of observations made in a case of disk herniation with compression of the fifth lumbar root.

As pointed out by Wohlfart earlier,[9] analogous conditions must be present in peripheral nerve injuries. The associated movements following a facial neuritis can be explained as the result of sprouting or faulty regeneration. One and the same nerve fiber may give off branches to facial muscles situated widely apart and, for instance, cause elevation of the corner of the mouth on contraction of the orbicularis oculi. Certain associated movements of extrinsic eye muscles following lesions of the oculomotorius nerve may be explained in a similar way.

The electromyographic findings in partially denervated muscles can also be explained by sprouting. The amount of denervation potentials in such muscles is often surprisingly small, a fact which is readily explained by the rapid re-innervation of denervated muscle fibers.

The increased duration of action potentials in the early stages after partial denervation in poliomyelitis, for example, can probably be explained by the increase in size of the remaining motor units and the small diameter of the collateral sprouts. This possibility was mentioned previously.[28]

Sprouting can evidently cause widespread giant motor units, a fact which must bear upon so-called synchronization in electromyography, that is, the appearance of synchronous potentials in muscle regions widely apart from one another. It is natural that potentials recorded from different parts of one and

the same unit should be synchronous. This does not imply that synchronization may not sometimes have another explanation, as advocated by Buchthal and co-workers.[29] It should also be pointed out that collateral sprouting in motor nerves has its analogy in the phenomena in sensory nerves described by Weddell, Guttmann, and Gutman.[30]

Finally, there is fairly good reason to suppose that some degree of sprouting is normal with increasing age. It has been stated[31] that the number of nerve fibers in the spinal roots decreases with increasing age. If this be true, the gaps in the muscular innervation must apparently be filled by sprouting. Wohlfart[32] pointed out that a disseminated neurogenic atrophy may sometimes be found in muscles from elderly persons. In such cases, it must be assumed that the degree of senile loss of ventral horn cells is so great that sprouting does not suffice to lead to complete re-innervation.

SUMMARY

Observations made in an investigation of verified amyotrophic lateral sclerosis suggested the following conclusions.

1. Successive destruction of motoneurons is accompanied by collateral sprouting from surviving nerve fibers, with consequent re-innervation of many muscle fibers.

2. This sprouting delays weakening and wasting of the muscles involved.

3. In many respects, the histologic picture of collateral sprouting in amyotrophic lateral sclerosis resembles that of nerve fiber regeneration following division of a nerve.

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■ The anterior columns of the spinal cord have, without doubt, a special connection with the anterior roots of the spinal nerves, and an all-important part to play in voluntary movement; and yet this cannot be said of them, as was formerly supposed, in every part of their course. The power of voluntary movement on the same side of the body, in the muscles behind the section, is altogether destroyed when one of the anterior columns is cut across, unless the cut be in the part which lies immediately below the anterior pyramid of the medulla oblongata; and the same result happens when the adjoining lateral column is cut across where it lies side by side with that part of the anterior column which may be cut across without giving rise to paralysis. It is plain, in fact, that in the uppermost part of their course the anterior columns have not that intimate connection with the anterior roots of the spinal nerves, and that all-important part to play in voluntary movement, which they evidently have everywhere else. And it is also plain that the anterior columns have somewhat to do with sensation as well as with voluntary motion, for it is a fact that a certain degree of numbness is always produced by the injuries which give rise to paralysis.

C. B. Radcliffe in *On Diseases of the Spine and of the Nerves*, published in 1871.

CLINICAL PATHOLOGIC CONFERENCE

E. P. Richardson, Jr., M.D. Section Editor

Presented by *Joseph M. Foley, M.D. and Charles A. Kane, M.D.*

CASE PRESENTATION

A 54 year old white woman was admitted to the fourth medical service of the Boston City Hospital on September 21 and died on September 25, 1952. Her chief complaint at admission was headache for one year, worse in the week before admission.

She was first admitted to the Boston City Hospital in 1943 for the birth of her seventh child. This occurred without complications, except that her blood pressure was found to be 220/120. She signed out against advice and, as far as is known, had no further difficulty until one year before admission when she consulted a physician because of headaches. A diagnosis of high blood pressure was made. She was given pills to take, as well as digitalis, and a low-salt diet was started. She stopped the diet and digitalis a few months before admission. The headaches persisted. They were intermittent, lasting usually 15 to 30 minutes, generally bifrontal, and sometimes could be relieved by Bromo-Seltzer.

A little over a week before admission she caught cold and had coryza and cough. For three days prior to admission the headaches became increasingly severe and were constant for at least the day before admission. On the day of admission she vomited three times and the headache became much more intense. Her physician referred her to the hospital.

Physical examination showed temperature 101.6° F., pulse 88, respirations 24, and blood pressure 255/130. She was a very obese middle-aged woman, complaining of throbbing frontal headache. There was no rash and no adenopathy. The retinal vessels were slightly narrowed and there was slight venous engorgement, but no papilledema. The thyroid was palpable, "perhaps slightly enlarged." There were fine crepitant inspiratory rales at the right base posteriorly and laterally. The heart was enlarged to the left anterior axillary line. There was a grade 3 harsh aortic systolic murmur transmitted to the apex and the neck. The abdomen was very obese. There was a moderate-sized urethrocele, an indurated cervix uteri, and a profuse white vaginal discharge. There were mild varicosities of the legs and a trace of pitting edema over both feet.

She was alert and oriented, although complaining of pain. It was noted that there were no signs of meningeal irritation, strength was normal, all deep reflexes were normally active without clonus, and both plantar responses were flexor.

Laboratory work on admission showed hemoglobin 13.0 gm. and white blood count 12,750, with 85 per cent polymorphonuclear leukocytes. The urine was negative except for a trace of albumin. The blood urea nitrogen was 15 mg. per cent.

Hospital course. The following morning she was found to have a paralysis of the right side. At this time blood pressure was 276/142, and she was started on Veriloid, 1 mg. four times daily. She was stuporous and mumbled incoherently. When asked the date, she kept repeating "52, 52, 52 ---." She was able to respond to simple commands, such as "Close your eyes," but more often she failed to respond. The pupils were round, regular, and equal, and reacted briskly to light. There was

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ptosis of the left lid and the left eye deviated laterally. There was a supranuclear right facial weakness and a complete paralysis of the right arm and leg with mild spasticity. All the deep reflexes were very brisk, and there was a right Hoffman sign and a right extensor plantar response. There appeared to be no deficit to pinprick. The neck was stiff. Kernig's sign was present bilaterally.

A lumbar puncture done at this time showed an initial pressure of 360. There were 160 white blood cells, of which 133 were polymorphonuclear leukocytes, and 50 red cells. The total protein was 174 mg. per cent. Sugar was 67 mg. per cent.

On the third hospital day she was seen by the neurologic consultant, who noted that she was very lethargic. She understood commands and obeyed occasionally. There was no withdrawal from a threat in the right visual field. The right arm was flaccid. Both legs were extended and spastic. There were bilateral ankle clonus and bilateral extensor plantar responses. There was a grasp reflex on the left. She responded to painful stimulation by wincing. The eye signs were the same as the day before.

On the fourth hospital day she was deeply comatose, with complete flaccidity of all muscle groups. There was no response to even the most painful stimuli. The pupils, although very much constricted, still reacted to light. The neck was no longer stiff. The right plantar response was extensor; there was no response on the left.

On the fifth hospital day respirations ceased, but pulse continued at about 90 per minute. Artificial respiration was kept up for about one and a half hours, after which no heart sounds were audible and she was pronounced dead.

On the second hospital day the temperature had dropped to 98° F., then rose to the 100° to 101° range where it stayed for the rest of her course. Blood pressures remained at about the level of admission until the last day when they fell to the 150/100 range. A urine done on the day before death showed 3+ albumin. A white blood count on the third hospital day showed no change from that on admission. No further lumbar punctures were done.

CLINICAL DISCUSSION

DR. CHARLES KANE: The problems presented for consideration in this protocol may be approached first by establishing the probable anatomic locations of the lesions and then reviewing possible pathologic explanations for the clinical and cerebrospinal fluid findings.

As I see it, the patient's terminal illness is not necessarily related to her long-standing hypertension. It would appear to me that the final illness evolved in three stages, beginning with a nonspecific upper respiratory infection about two weeks prior to death. This was soon followed by increasingly severe generalized headache with emesis, which could have been due to a "hypertensive crisis" except that there was no significant elevation of diastolic pressure, papilledema, retinopathy, albuminuria, or azotemia.

The next phase was ushered in on the second hospital day by the sudden development of right-sided weakness, stupor, and dysphasia without hemianesthesia, suggesting a fairly large, subcortical lesion in the left frontotemporal area. At the same time, the eye signs indicated an external ophthalmoplegia, with normal pupillary responses. This can only be due to a midbrain lesion on the left since, in my experience, the pupillary-constrictor fibers of the third nerve are far more sensitive to compression (as in an uncal herniation) than are the oculorotary fibers. At the same time, the clinical and cerebrospinal fluid signs of meningeal irritation became apparent. These are consistent with meningeal inflammation but not necessarily infection.

I would interpret the left-sided grasp reflex as evidence of extension of the process across the corpus callosum to the right medial frontal area. The terminal failure of respiration with continued heart action is entirely consistent with evolving medullary compression from herniation of cerebellar tonsils through the foramen magnum.

Anatomically, therefore, I should expect to find: 1) a large, destructive lesion beginning in the central part of the left hemisphere; 2) a second similar lesion on the right, spreading by contiguity via corpus callosum; 3) a left midbrain lesion; and 4) medullary compression by a "cerebellar pressure cone."

What are the pathologic possibilities which might account for the fulminating

course and the cerebrospinal fluid polymorphonuclear response with high protein, normal sugar, and high pressure, but without gross blood or evidence of infection? Unfortunately, a zinc sulfate test for gamma globulin was not done on the spinal fluid, although this would have been of great interest in this case.

The differential diagnosis should certainly include the possibilities of subdural empyema (from purulent frontal sinusitis), cortical thrombophlebitis, suppurative encephalitis (subacute bacterial endocarditis), brain abscess, necrotic glioma, cranial arteritis, "brain purpura," and the various possible cerebrovascular complications of hypertension.

From a practical point of view, most of these patients are seen by neurosurgeons as brain abscess or tumor suspects, and many reported in the recent literature have come to craniotomy. This is not difficult to understand, since the asymmetric swelling of the white matter of the centrum semiovale may cause displacement of the anterior cerebral artery on cranial arteriography. The electroencephalogram may or may not be abnormal.

In my own experience with five similar cases, the most troublesome differential diagnosis is the exclusion of a focal septic intracranial process, such as brain abscess or subdural empyema. In two patients heart murmurs brought up the possibility of a bacterial endocarditis with multiple areas of suppurative encephalitis. Since these conditions are remediable, one must first exclude them before seriously considering more esoteric possibilities.

I believe all the necessary clinical criteria are present in this instance for a diagnosis which has many synonyms, but which is commonly called "acute hemorrhagic leukoencephalitis"[1] in Australia and England and "acute necrotizing hemorrhagic encephalopathy,"[2,3] in this country. This is now regarded as most likely a form of "neuro-allergy," that is, an intense, Arthus-like reaction of cerebral white matter (and both grey and white matter of brainstem) to some unknown antigen. The end result is a pathologic picture resembling a mixture of Schilder's disease and acute disseminated encephalomyelitis. Because of the basic tissue response, one would be interested in a trial of intrathecal hydrocortisone or oral anti-inflammatory steroids (Metacortandracin). One personal experience with parenteral corticotropin was unfavorable, but inconclusively so because treatment was delayed.

Koprowski and Jervis[4] noted that guinea pigs treated with a heterologous emulsion of brain plus adjuvants and surviving would react violently to a second intracerebral inoculation of the same material. The animals dying in less than a week showed focal hemorrhagic and necrotic lesions, while those surviving over a week showed focal demyelination where inoculated and disseminated foci of demyelination elsewhere in the nervous system.

I would feel, therefore, that the preceding upper respiratory infection, rather than the hypertension, in this case in some obscure manner brought about a delayed antigen-antibody reaction resulting in that kind of necrosis of white matter which is called "acute necrotizing encephalomyelopathy." The accompanying massive brain-swelling, leading to a foramen magnum "pressure cone," then caused death by medullary compression.

PATHOLOGIC DISCUSSION

DR. JOSEPH M. FOLEY: As Dr. Kane has so ably concluded, no significant lesions related to the final illness were found except in the brain. The brain was examined after formalin fixation. The dura was natural and the venous sinuses were patent. The leptomeninges showed no exudate grossly. Both hemispheres were swollen. When the falx was removed, some subfalcial displacement of the left cingulate gyrus was discovered, especially in its frontal region. At the base of the brain there was bilateral tentorial herniation of mild degree, more pronounced on the left. The vessels at the base

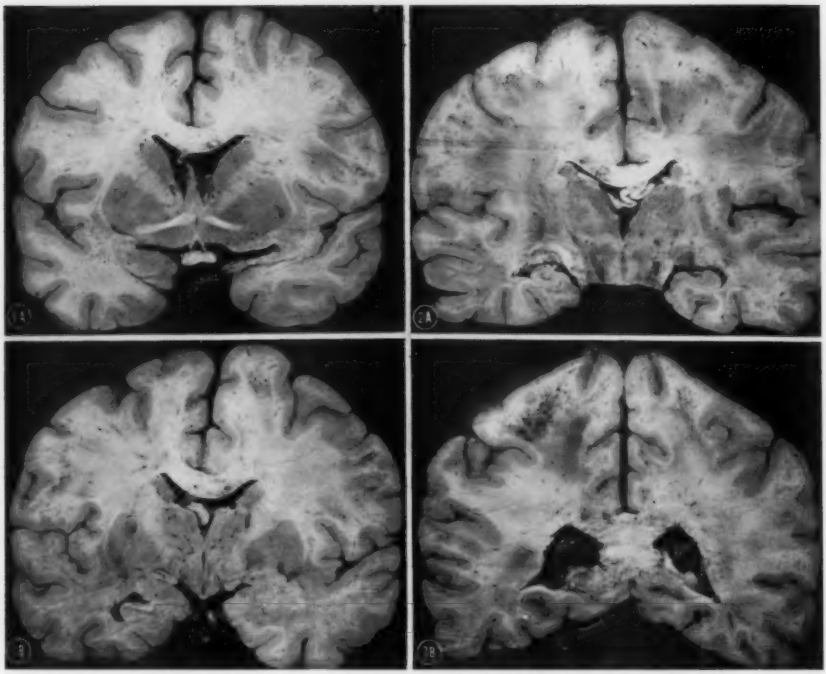

FIG. 1. The swelling is more pronounced in the left hemisphere (right of the photograph). The gross lesions are in the subcortical white matter, but generally spare the immediately subcortical zone. Largely unilateral at the level of the chiasm (*A*), the process becomes bilateral in more posterior sections (*B*). FIG. 2. At these levels, the change is bilateral, diffuse, and more frankly hemorrhagic. The corpus callosum is more involved posteriorly than anteriorly. In *A* there is some involvement of cerebral cortex.

were moderately atherosclerotic, but no occlusions were found on multiple sections.

The brain was cut in coronal section. There was a pronounced swelling of the white matter of both cerebral hemispheres, more so on the left. There was discoloration of the central white matter extending throughout the entire hemisphere, but most pronounced in the subcortical white matter where the brownish discoloration merged into a series of petechial hemorrhages. This relatively minor degree of change in the frontal region became progressively more intense as the posterior frontal region was approached. The most severe degree of change was in the centrum semiovale of the left parietal lobe in the parasagittal region. There were multiple petechial hemorrhages in the brainstem extending up into the peduncles. These spared the tegmentum of brainstem and seemed to have a particular predilection for the white pathways, but the central white matter of the cerebellum was spared.

This is the gross appearance of the lesion which Dr. Kane has indicated. This is acute necrotizing hemorrhagic encephalopathy.

The most significant microscopic changes were related to the blood vessels and the areas immediately surrounding them. The involvement was almost exclusively in the white matter, although some change was

FIG. 3. The basis pontis and peduncles are spotted with petechiae, many of them confluent. Histologically, the most recent changes were found in this area.

present in the nuclei of the pons and midbrain, and there was a rare overflow of lesions into cerebral cortex.

The first kind of change, minimal in the cerebrum and maximal in the pons and in the cerebellar peduncles, was an extravasation of red blood cells into the perivascular areas. The red blood cells in the pons and cerebellar peduncles were for the most part fresh, and only in a few places was phagocytic reaction present. In the white matter of the cerebrum a rare instance of such recent perivascular bleeding was seen, but more commonly there were red blood cells or hemosiderin in phagocytes in the perivascular areas.

The second kind of change consisted of a perivascular accumulation of inflammatory cells of varying types and intensity, only rarely restricted to the immediate perivascular space, and most commonly extending out into the surrounding tissues. In the brainstem this cellular reaction consisted almost entirely of polymorphonuclear leukocytes, with a few lymphocytes and large mononuclear cells. In the cerebrum the polymorphonuclear leukocyte component was slight, and the cells were largely round cells. In some places in the cerebral white matter only proliferating astrocytes surrounded the vessel. Histiocytic macrophages, usually fat-filled but, as noted above, sometimes hemosiderin-filled, were prominent in the inflammatory exudate in the cerebral white matter, and pleomorphic microglia were abundant throughout the cerebral white matter.

A mixture of polymorphonuclear leukocytes and small and large round cells with many macrophages were seen in the leptomeninges, especially around vessels.

The vessels around which these reactions took place both in brain substance and in the leptomeninges were generally smaller veins and venules, to a lesser degree smaller arteries and arterioles. Occasionally cells could be found in the perivascular spaces of some of the larger veins and arteries. Endothelial proliferation, although present in some areas, was not a constant finding. There were no thrombi in any vessels. Only in the brainstem was there any fibrin, and there only rarely and to a slight degree. It was restricted to the wall of the vessel and a narrow zone of perivascular tissue. This is in contrast to other reported cases of acute necrotizing hemorrhagic encephalopathy in which the fibrin exudate was extremely prominent. Such minimal fibrin exudate may represent the slower evolution of the inflammation in this patient.

The special stains showed loss of myelin in the areas of cellular inflammation. Axis cylinders were also destroyed in most areas, and ballooning and fragmentation of fibers was a constant finding. In the motor cortex there were many large pyramidal cells which were undergoing chromatolysis.

The inflammatory reaction of this disease in this patient is represented by many dif-

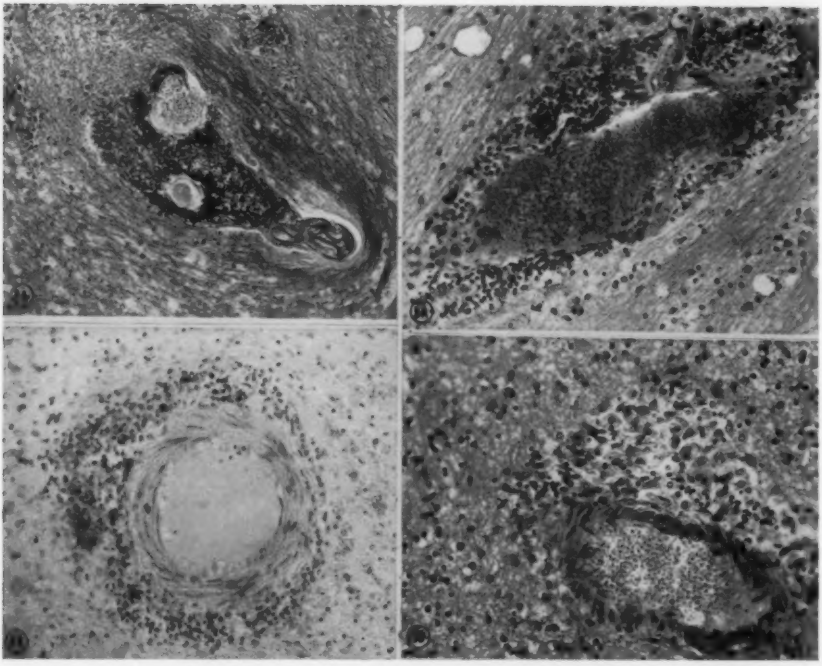

FIG. 4. A. Left parietal white matter. The perivascular reaction does not involve the total circumference. The predominant cell is the histiocyte, with some lymphocytes. Hematoxylin-eosin stain. *B.* Nuclei pontis. The perivascular reaction is for the most part neutrophilic and lymphocytic. Eosin-methylene blue stain.
FIG. 5. A. Nuclei pontis. There are a few extravasated red cells, as well as a neutrophilic perivascular reaction. Eosin-methylene blue stain. *B.* Brachium pontis. This is one of the infrequent instances of fibrin exudate in the vessel wall, extending out into the perivascular space. PTAH stain.

ferent stages, indicating activity of the process not only from the onset of symptoms eight days before death, but also as recently as one or two days before death. The distribution of lesions suggests a kind of cephalocaudal extension, although of multifocal origin. Unfortunately the spinal cord was not available for study.

Dr. Kane has discussed the prevailing idea about the pathogenesis of this disorder. Virus studies were not attempted in this case, but they have been unrewarding in other cases, and the striking sparing of gray matter argues against a viral etiology. Although the process in its totality is indeed necrotizing, there are some areas, especially at the periphery, which are more reminiscent of the non-necrotizing perivascular reactions of postinfectious encephalomyelitis. The distribution of the lesions and their mode of progression are like Schilder's disease, which is, of course, a much more slowly progressive inflammatory process.

This class of disease is poorly understood. If it is an inflammatory, non-infectious necrosis, caused by a perverse happenstance of abnormal immunology, it would be reasonable to try to take advantage of the inflammation-suppressing properties of the steroid hormones. My own difficulty in this regard is that, although I have made

the diagnosis antemortem, I have never been able to make it with a high enough degree of certainty to exclude an infectious process, and the patient is dead before intracranial suppuration or infectious granuloma can be excluded.

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■ Pathology is the basis of every rational system of therapeutics. That, possibly, the greater part of our most effectual treatment is at present empirical I would not deny, but that therapeutics will become rational is what we all hope. To those who are quietly and laboriously working at what may, superficially looked on, seem to be obscure pathological problems, steady advances in diagnosis and rational therapeutics will be chiefly owing. It is evident that, for rational therapeutics, we must know what there is to be treated. No man in our profession deserves greater credit than the pathologist – including, of course, the clinical pathologist, and never forgetting the medical officer of health. The medical officer of health is the pathologist of the Social Organism, and deserves the highest social recognition. Speaking more narrowly, tacitly assuming the obvious qualifications, the best practitioner, perhaps not the most confident one, is he who has carefully made most post-mortem examinations. I do not mean him who stops here, who stops in a stage which is rather to be called one of morbid anatomy than of pathology. But a man must begin here – must begin here to learn for himself, at any rate. The best knowledge for practice is what a man gets for himself. The only way of being thoroughly practical is to face the facts, to get verification or disproof of our opinions. A post-mortem examination never flatters us. If, for an example, we diagnose tumour of the cerebellum during the life of a patient, we may, post-mortem, find one in the anterior cerebral lobe. Such a rap on the knuckles is good for us. It makes us less confident, and teaches us to be more careful. A post-mortem examination may tell us that we have been treating a patient with useless, perhaps with injurious, drugs.

J. Hughlings Jackson in *Address on Pathology*, published in 1882.

CASE REPORT

Succinylcholine Chloride in Electroencephalography

Kittridge Anderson, M.D. and Ian C. Funk, M.D.

ONE COMMON annoying and perplexing feature of clinical electroencephalography is the muscle movement artifact. These artifacts can obscure genuinely abnormal electrical activity or, even more disconcerting, can misleadingly resemble true wave or spike-wave dysrhythmia.

In so far as the authors have been able to ascertain, the case to be presented is the first one in which a curare-like drug has been used in human electroencephalography exclusively to eliminate this muscle movement artifact. It was found that succinylcholine chloride could be used to advantage in those patients who had seizures during Metrazol activation electroencephalography. In this way the abnormal cerebral electrical activity during a Metrazol-induced seizure can be recorded from the scalp without electrical interference from the muscle movement of the seizure.

The following case illustrates the manner in which this technic was developed.

A 27 year old Negro was admitted to the Albany Veterans Administration Hospital on January 12, 1956 for evaluation of his convulsive disorder. These seizures started in 1952; however, there was a questionable history of childhood seizures. For the year prior to hospitalization he had had approximately two convulsions a week. During hospitalization he had several seizures which were witnessed by the ward nurses, and their report confirmed the patient's description of a generalized and symmetric, clonic-type convulsion with tongue biting and urinary incontinence. Dizziness and headache were his usual prodromal symptoms.

There was a family history of convulsions; the patient's father and one of the patient's brothers had had convulsions. The patient had been a professional boxer for a number of years and had been "knocked out" several times for periods up to five minutes. As the result of an automobile accident in 1948, he was rendered unconscious for approximately eight hours.

No significant abnormalities could be found on either general or neurologic examinations.

The routine blood and urine tests done during hospitalization were normal. The serologic test for syphilis gave a negative reaction. Pneumoencephalography on February 7, 1956 revealed a normal cerebrospinal fluid initial pressure and normal protein. The pneumoencephalogram was interpreted as showing a slight degree of diffuse enlargement without displacement of the left lateral ventricle.

A routine awake electroencephalogram was done on January 19, 1956. This tracing was composed primarily of low voltage 10 per second activity which was interpreted as normal. Since the routine record was normal, a Metrazol activation electroencephalogram (figure 1, A 1 and 2) was done on January 27, 1956. The pre-Metrazol part of the tracing was comprised of normal low voltage 10 per second activity. For this procedure a 0.05 per cent solution (50 mg. per cc.) of Metrazol was administered intravenously at exactly 2 cc. per minute (100 mg. per minute). After an amount

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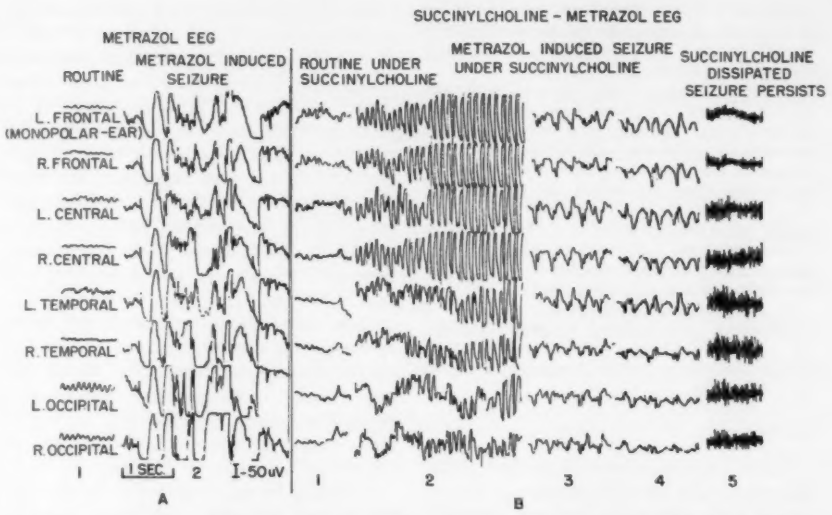

FIG. 1. *A*. Electroencephalogram January 27, 1956: 1. Normal tracing before the administration of Metrazol. 2. Tracing which shows admixture of seizure activity and muscle movement artifact after the intravenous administration of 400 mg. of Metrazol. *B*. Electroencephalogram February 17, 1956: 1. Routine tracing which shows normal rhythm during paralysis stage of succinylcholine. 2. Twenty-four seconds after Metrazol (500 mg.) administered; high voltage eight per second seizure activity appeared while the patient was motionless from succinylcholine. Compare with *A* 2. 3. One minute after Metrazol administered. Still paralyzed from succinylcholine. Note repetitive spike and wave activity. 4. Four minutes after Metrazol administered; repetitive spike and wave activity persists. Clonic movement of feet appeared. 5. Succinylcholine effect dissipated. Note muscle artifact due to continuing seizure.

as small as 1 cc. had been given, high voltage spike-wave discharges appeared. With further administration of Metrazol, long runs of a repetitive spike and wave complex appeared.

During the time of this latter activity the patient had a seizure. This seizure commenced with unconsciousness, followed by a patting movement of his left hand. Soon thereafter his head, with eyes turned down, rose from the bed and there were running movements of his legs. A severe emprosthotonos developed which changed to a slight pleurothotonos to the right. In a few seconds the patient stiffened out. His arms went into a marked flexion tonus which had a clonic component. The patient had a usual degree of frothing at the mouth and postictal confusion. A total of 400 mg. of Metrazol had been given.

Although the electroencephalogram during this seizure was composed of what appeared to be genuine spike-wave discharges, the muscle movement artifacts produced by the seizure made reliable interpretation impossible.

On February 17, 1956 he was again subjected to a Metrazol activation electroencephalogram; however, this time it was performed while the patient was paralyzed by intravenously administered succinylcholine chloride.

After a relatively normal routine record had been made, 50 mg. of succinylcholine chloride was administered intravenously over a 20 second period of time. Approximately 40 seconds later, just before the patient was totally immobilized, 500 mg. of Metrazol was administered intravenously over a period of 90 seconds. In order to avoid delay and to assure an intravenous route, both of these drugs were injected into the rubber tubing of an intravenous drip of sterile saline which had been set up in advance of this procedure.

While the patient was paralyzed by the succinylcholine and before the Metrazol had taken effect, there was a short interval of normal tracing (figure 1, B1). Within a few seconds there was a sudden appearance of high voltage eight per second activity. Although the patient lay

immobile, it was evident he was in the midst of a seizure at this point for he was frothing at his mouth. Respiration was maintained through bag-breathing with oxygen.

For the subsequent four minutes, while the patient was still paralyzed from the effects of succinylcholine chloride, the tracing showed synchronous spike-wave discharges which decreased in frequency from three waves per second to two waves per second (figure 1, B3 and 4). Within seconds, and before this activity had ceased, movement returned to his feet and then to the rest of his body with resulting obliteration of the previously described dysrhythmia by seizure movement artifact (figure 1, B5).

The patient was quieted with 4 grains of intravenously administered Luminal. He did not suffer any adverse effects from this procedure and was therefore discharged on February 27, 1956.

DISCUSSION

Curare and synthetic curare-like drugs have been used for several years in experimental work with animals where immobilization without anesthesia is essential. These drugs have also been used to advantage in psychiatry to protect patients undergoing electroconvulsive therapy from unnecessary bodily injury during the seizure.

As far as could be ascertained, the use of electroencephalography on curarized patients was first reported in 1952 by Schmidt and co-workers[1] who used it to eliminate the seizures in tetanus while simultaneous electroencephalograms and electromyograms were taken. Shea[2] used electroencephalography in the curarized patient to determine the level of consciousness after the initially administered Pentothal had dissipated itself under curare. The authors were unable to find a previously reported case in which a curare-like drug was used to eliminate the movement of a Metrazol-induced seizure so that an artifact-free electroencephalogram could be obtained for study.

Before curare or one of the synthetic curares can be used in clinical electroencephalography for diagnostic purposes, it should be shown to have no significant effect upon the cortical electric activity. On this point there is still controversy as to what effect these compounds have on the electroencephalogram in animals and in humans.[2–5] However, sufficient investigation has been done along these lines to state that these drugs do not produce significant excitatory or inhibitory effects upon the cortex to give false positive or false negative electroencephalograms.[2,3] In our own experience and from the observations of others,[1–3] the electroencephalogram in curarized humans remains essentially unchanged. This is especially true with the shorter acting synthetic curare-like drugs such as succinylcholine.[3]

It is not within the scope of this paper to discuss the uses or merits of Metrazol in clinical electroencephalography. In our own experience electroencephalographic dysrhythmias induced by 500 mg. or less of intravenously administered Metrazol are indicative of a convulsive diathesis.

It should be mentioned that in this case the patient did not receive any sedation before the test. Although sedation with one of the short-acting barbiturates would be desirable to allay the anxiety produced by the paralysis from succinylcholine, this same sedation would inhibit the effects of Metrazol and make electroencephalographic interpretation worthless.

Actually, this procedure has a wider application in clinical electroencephalography than depicted. It can be used in any instance of routine electroencephalography where muscle tension or movement artifact produces sufficient electrical interference to invalidate interpretation of the tracing. Trial of this procedure seems warranted in disturbed, restless, and otherwise uncooperative patients where electroencephalography is indicated, as well as in the reassessment of electroencephalographic findings in other disease states with movement disorders such as the choreas, tics, and tremors.

SUMMARY

1. A single case is presented in which succinylcholine is introduced as a valuable adjunct to Metrazol activation electroencephalography.

2. The manner in which succinylcholine chloride is used to eliminate the seizure movement artifacts is outlined.

3. Other uses of succinylcholine chloride in clinical electroencephalography are proposed.

Miss Harriet Morlock, chief technician, Electroencephalography Laboratory, gave technical assistance in this study.

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■ Vesalius denies the existence of the net-like plexus, which he, in derision, calls blessed and wonderful; asserting that it was a creature of Galen's imagination. He reprobates what he calls the nonsense of the Greeks, who pretend to learn the structure of the human body from the dissection of the bodies of brute animals, following the wild fancies of their own imaginations; yet in his account of the nervous system, he has not been able to point out more than two or three errors of Galen, the greatest part of whose anatomy and physiology on this subject is under the necessity of adopting. With Galen, he considers the brain as the seat of the rational soul, which acts on the sentient and moving parts by the animal spirit and nerves; and with Galen he thinks that from the blood-vessels, in their winding course, the vital spirit is formed, from which, with a portion of air insinuating itself into the brain, the animal spirit is first prepared, which is afterwards elaborated in the ventricles of the brain, whence a portion of it is carried into the ventricle of the cerebellum, and into the spinal marrow, and so to the nerves arising from the spinal marrow, the spirit passing from the other ventricles into those nerves which have their origin near to them, and by them to the organs of sense and voluntary motion.

John Cooke in *A Treatise on Nervous Diseases*, published in 1824.

ROBERT WARTENBERG, M.D., 1887-1956

IT IS WITH HUMBLE SPIRIT that one writes of a departed friend and colleague with whom one has worked and collaborated for over a period of 20 years. Dr. Robert Wartenberg, a fellow of the American Academy of Neurology and an associate editor of NEUROLOGY, died of a heart illness on November 16, 1956.

Born in Grodno on the German border of Russia in 1887, he won his medical degree "magna cum laude" from the University of Rostock in 1919, worked under such eminent men as Prof. Nonne in Hamburg and Prof. Foerster in Breslau, married the Baroness Isabelle von Sazenhofen in 1929, became physician-in-chief of the Nerve Clinic of Freiburg, and was made a German equivalent of associate professor of neurology in Freiburg in 1933.

With the rise of Hitler to the Chancellorship of the Reich in 1933 and the tightening of Nazi control over Germany in the next two years, many, including Dr. Wartenberg, fled the country in 1935.

Doctor Wartenberg started his second career in our midst in 1936 and rose successively through the clinical ranks at the University of California School of Medicine (San Francisco) until in 1952 he was appointed clinical professor of neurology. Two years later he retired, but he continued to serve in a part-time capacity and maintained his editorial work and writing until the time of his death. Through his influence, the department of neurology's program of teaching and scholarly research was considerably enriched. To his students, he was an inimitable, stimulating, and beloved professor. Although always respecting his European scientific and cultural background, it was his enthusiastic acceptance of American ideals and American neurology which endeared him to his colleagues in this country.

The list of his graduate medical lecturing

engagements, his editorial appointments and activities, his books and scientific writings, and his international honors is long and obviously bespeaks an illustrious career. Among his numerous contributions, perhaps his book on *Examination of Reflexes*, which has been translated into seven languages, was his most outstanding work. It represents a simplification of an extraordinarily complicated literature and exemplifies Dr. Wartenberg's scholarly capacity at its best.

He was elected to honorary membership in eight neurologic societies, including the Spanish Neurological Association, the German Societies of Neurology and Neurosurgery, Rio de Janeiro Society for Neurology, Neurosurgical Society of Italy, Society for Psychiatry and Neurology of Vienna, and the Argentine Society of Neurology, Psychiatry, and Neurological Surgery. He was also an associate editor of three neurologic journals at his death.

The high dramatic quality of his teaching, his infectious enthusiasm and good humor, the scholarly thoroughness and accuracy of his writings, and the sharpness of his tongue and pen in his staunch advocacy of high standards in neurology were well-known to all who came in contact with him. Only those who knew him well, however, understood the true Robert Wartenberg.

He has been referred to by a friend as a "glorious paradox," and indeed an excelcent case can be made for this view. In spite of his Germanic thoroughness as an editor and author, he was the acme of brevity in his clinical reports. In spite of the intensity of his enthusiasm, he was a shrewd and practical person.

In spite of his Nazi persecution, he never referred to this and even defended those German colleagues who he thought were wronged by post-war prejudices. International collaboration and understanding was one of his dearest causes and it was with relish that he accepted the invitation to return to Freiburg in 1954, even though it was a questionable thing to do from the standpoint of his already precarious health.

In spite of his dramatic qualities and his love of the limelight, which represented his method of living out his role as a teacher, he was simple and humble at heart. He had no ambitions in the sense of money, luxuries, power, or social position.

In spite of his sharp tongue and biting criticisms, he meant no personal offense and fundamentally was not destructive. He was a crusader against lax standards and inaccuracy in the field of neurology which he loved. For every academic toe he stepped upon publicly, he advised and helped one hundred other physicians quietly and privately.

Doctor Wartenberg, however, was something above and beyond all this. Perhaps a slight modification of the aphorism of the Earl of Chesterfield, "Whatever is worth doing at all, is worth doing well" *and wholeheartedly*, best expresses the spirit of Dr. Wartenberg. The addition of "and wholeheartedly" is essential in the case of Dr. Wartenberg, since he truly lived with gusto. He despised mediocrity, half-measures, and a compromise of principle. To those of us who plod along in our daily tasks and too often compromise with what we call necessity, his zestful "By the great Babinski, no!" was a heartening tonic. Who else but Robert Wartenberg, in spite of repeated warnings from his physician, could carry on the good fight until the end? Within two hours after he had completed his last book, he quietly entered the hospital, knowing that it was the end. Who else in his last days, while speaking to his physician of his own condition, would raise his hand in his typical gesture and say, "It is typical, a terminal case," and still continue to wonder about ways and means to assist a friend in Budapest?

In his passing, the American Academy of Neurology, the University of California, and in fact the whole of clinical neurology have lost one of their most colorful figures, an inspired teacher, and a staunch friend.

ROBERT B. AIRD, M.D.

Neurology

BOOK REVIEWS

Peripheral Nerve Injuries

Nerve Injuries Committee of the Medical Research Council, edited by H. J. Seddon, C.M.G., D.M., F.R.C.S. 1954. London: Her Majesty's Stationery Office. American Agents: British Information Service, 80 Rockefeller Plaza, New York 20, N. Y. 451 pages. $10.00.

In 1920, following the first World War, the Medical Research Council's Committee upon Injuries of the Nervous System prepared a report on peripheral nerve injuries, which was revised and reprinted in 1942. This contained an account of the clinical features of nerve injury and the phenomena of recovery and also discussed the principles of operative treatment, electrotherapy, and splinting. The conclusions which were reached by the distinguished body of clinicians who participated in the study were that secondary suture was the most reliable method of operative repair, nerve grafting was not justifiable, the value of neurolysis was doubtful, and the nature of causalgia was still undetermined.

The committee has now put out a new and much more comprehensive report which is different from the original one in that no attempt has been made to present a systematic account of the diagnosis and treatment of nerve injuries, but the investigative aspects are considered in much more detail.

It is brought out in this book that diagnosis of peripheral nerve injuries is made much more precise by a study of clinical manifestations, together with that of disturbances of autonomic function, sweating, and vasomotor control; by the use of nerve blocking and of nerve and muscle biopsy; and by detailed electrical studies including electromyography. The histopathology of nerve injury is dealt with in detail, and rates of regeneration have been worked out with some precision. Although the pathology of causalgia is still unsolved, a reasonable hypothesis of its causation is postulated. On the basis of prolonged observation of many cases, it is concluded that the best treatment for a severed nerve is early secondary repair; primary suture is no longer regarded as ideal even in aseptic wounds. In cases in which there has been an extensive gap in the continuity of nerves, re-examination of the possibilities of repair by grafting has been carried out. Homogenous nerve grafting has proved unsuccessful, but the results of autogenous grafting are encouraging.

This is probably the most detailed study and review of peripheral nerve injuries available. While detailed descriptions of individual nerve syndromes are not included, the studies give many important contributions to the investigation, pathology, and mode of treatment of injuries of the peripheral nerves. The many outstanding and distinguished members of the Nerve Injuries Committee, as well as the scientific reputation of the individual contributors, should be a reliable indication of the authenticity of this book.

R. N. DE J.

A Clinical, Pathological and Genetic Study of Multiple Neurofibromatosis

Frank W. Crowe, William J. Schull and James V. Weel. 1956. Springfield, Illinois: Charles C Thomas, Publisher. 181 pages. $5.00.

THIS STUDY, a cooperative project carried out in the department of dermatology and the Heredity Clinic of the University of Michigan, is chiefly remarkable and valuable for the statistical and genetic analysis of a large number of cases of von Recklinghausen's disease. In all, 223 patients were available for study. Nothing is added either clinically or pathologically to what is already well known regarding the involvement of the central nervous system in neurofibromatosis, but certain facts are established about the cutaneous manifestations of the disease that are of direct interest to the neurologist. This is especially true with respect to the diagnostic validity of macular pigmentation. The authors have found that no less than 78 per cent of persons with neurofibromatosis, but no normal adults, bear six or more café-au-lait spots on the skin. They have formulated a diagnostic axiom to the effect that any individual with more than six caufé-au-lait spots greater than 1.5 cm. in diameter must be presumed to have neurofibromatosis. In the authors' experience, however, cutaneous pigmentation was less constant and extensive in patients with central nervous system involvement than in those with the peripheral form of the disease.

Biopsy of cutaneous tumors was carried out on 107 of the patients. The main points to emerge in the discussion of this material were that such tumors are essentially proliferations of the interstitial connective tissue of the nerves, mainly the endoneurium and perineurium, and that they frequently harbor large numbers of mast cells.

About one-half the patients were familial cases. The comprehensive genetic analysis of this group supports the generally accepted view that von Recklinghausen's disease behaves as a dominant trait, and suggests that sporadic cases are the result of mutation, with the highest mutation rate as yet known in man for a dominant trait. The frequency of the disease in the population studied was estimated to be .0003 to .0004, that is, one case for each 2,500 to 3,300 births.

This book represents a solid contribution to the literature of multiple neurofibromatosis.

R. B. R.

James Parkinson (1755-1824)

Macdonald Critchley, editor. 1955. London: Macmillan & Co. 268 pages. $4.50.

JAMES PARKINSON was born in 1755, and it is fitting that his bicentenary year should be marked by the publication of this small, interesting volume. His *Essay on the Shaking Palsy* was originally published in 1817, and the original text of the monograph is again made available in this book; with it are a few other essays which will serve to bring up-to-date our knowledge of Parkinson's disease.

Dr. Critchley, the editor, contributes a short introductory section in which he reviews our present day concept of Parkinson's disease, as it was first named by Charcot in 1884, and of parkinsonism secondary to other processes. He also speculates on the question of whether there is a diathesis or constitutional susceptibility toward the disease. Dr. W. H. McMenemey has prepared a detailed biographic account which gives some hitherto unknown information about Dr. Parkinson, who was a man of many interests and activities. Two very important contributions to the book are the section by Dr. J. Godwin Greenfield on the pathology of Parkinson's disease and that by Sir Francis Walshe on a clinical analysis of the paralysis agitans syndrome.

Dr. Greenfield brings up-to-date the concepts of the pathology, stressing the lesions in the substantia nigra, and states that the disease in its classic form is a systemic degeneration of a special type affecting a neuronal system whose nodal point is the substantia nigra. He expresses the belief that the cause of this degeneration is a problem whose solution may be found in enzyme chemistry or some other new field of investigation. Sir Francis Walshe, in his usual critical analysis of a clinical problem, stresses the fact that rigidity appears first in the proximal muscles and that slowness and limitation of motion are secondary to the rigidity. He states, further, that the cogwheel phenomenon and the tremor in paralysis agitans are essentially one in nature and origin and are abnormal degrees of the basic phenomenon present in all voluntary movement but accentuated in the presence of rigidity and slowness of movement.

From points of view of both the history of neurology and current and critical concepts of pathology and clinical symptomatology, this little book is a very valuable addition to the neurologist's library.

R. N. DE J.

The Relationship Between Syringomyelia and Neoplasm

Charles M. Poser. 1956. Springfield, Illinois: Charles C Thomas, Publisher. 98 pages. $3.50.

ALTHOUGH this is a small monograph, it is at the same time a singularly comprehensive review of one extremely important aspect of syringomyelia. The association of spinal cord tumor with syringomyelic cavitation is well known. The author has collected and collated 234 such cases appearing as scattered reports in the literature between 1867 and 1954. The labor has been done so well that other workers interested in the field will be spared repeating it. The book is not a mere catalogue of the cases, however. Relationships have been seen and presented in such a way that, out of this material, a most convincing case has been made for the thesis that syringomyelia is essentially a manifestation of a developmental anomaly associated with cellular and tissue metaplasia in a variety of forms. Of particular interest are the interrelations observed between syringomyelia, von Recklinghausen's disease, and the phakomatoses, a relationship so close as to suggest that all of these conditions are differing but frequently combined expressions of the same biologic perversion of development and growth.

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FEBRUARY 1957

101 Added to AAN Membership in Nov. and Dec. During November and December 1956, 101 additional physicians and scientists accepted invitations to AAN membership. These new members (all categories) are: S. Spafford Ackerly, Raymond A. Adams, Francis Adler, V. E. Amassian, John A. Anderson, S. T. Anvari, Herbert Bengelsdorf, Edgar A. Bering, Jr., Joseph Bernsohn, Michael E. Blaw, Jerome Block, Emanuel M. Bogdanove, Louis L. Boyarsky, A. E. Braley, Kenneth M. Browne, W. Jann Brown, Randolph K. Byers, Charles A. Carton, J. F. Casey, William P. Chapman, David Cowen, Frederick Crescitelli, Elizabeth S. Crosby, Elisabeth B. Decker, Alberto N. Delmar, Philip R. Dodge, Sheila Donahue, P. J. Doyle, Pierre M. Dreyfus, Teresita S. Elizan, Joseph F. Fazekas, Simeon L. Feigin, Charles H. Field, Eldon L. Foltz, Alfred M. Freedman, Stephen R. Fromm, Leslie H. Gaelen, Donald M. Gallant, Claude Gauthier, J. A. Gengerelli, A. L. Goodgold, Robert G. Grenell, Harry F. Harlow, Frank Harrison, Jack Hasson, Elwood Henneman, Arthur Hess, Walther Hild, Christopher A. Iannucci, W. H. Jeffreys, Abram Kanof, George Kelemen, Laibe A. Kessler, Wolff M. Kirsch, Walter R. Kirschbaum, Frederic J. Kottke, Lawrence S. Kubie, Henricus G. J. M. Kuypers, John I. Lacey, Martin G. Larrabee, Solomon J. Lederman, Gerard M. Lehrer, David P. C. Lloyd, Eugene W. Loeser, Jr., Cesare T. Lombroso, Irving Lorge, Florence I. Mahoney, Verne R. Mason, William T. McLean, Jr., Bernard Messert, Bernard Metz, Harold W. Mikkelsen, Brenda Milner, Kenneth S. Mills, Motoji Miyazaki, Robert S. Morison, Ntinos C. Myrianthopoulos, Richard Naef, Harold D. Paxton, F. A. Quadfasel, John Raaf, James B. Ranck, Jr., R. H. Rigdon, Charles E. Riley, Jerzy E. Rose, H. F. Scherrer, William A. Sibley, Rita Lynne Silver, Sam Silverstein, Jean Sirois, Ray S. Snider, Harry Sobotka, Louis Sokoloff, Daniel Lawrence Sutherland, August G. Swanson, Lewis Thomas, Charles Usher, Frank B. Walsh, John Woodard, Lewis Martin Wiener, and Robert E. Yoss.... Since the campaign for a larger and broader AAN membership began last May, 568 physicians and scientists have been added to the rolls of the membership committee.... Inquiries on AAN membership should be sent to Dr. Pearce Bailey, Chairman, AAN Membership Committee, National Institute of Neurological Diseases and Blindness, Bethesda 14, Maryland.

Kansas to Feature Postgraduate Course in Neurology

The University of Kansas Medical Center will hold a two-day postgraduate symposium type of course on a wide range of problems related to diseases of the nervous system. Complementing the Kansas neurologic staff, there will be a guest faculty to include Joe R. Brown of the Mayo Clinic, Joseph M. Foley of Harvard, Franklin R. Miller of the Snyder Clinic, Winfield, Kansas, and John A. Segerson of the Menninger Foundation.... Registration fee for the course is $30.00. All inquiries and communications should be sent to the Department of Postgraduate Medical Education, University of Kansas School of Medicine, Kansas City 12, Kansas.

* * * * * *

Reticular Formation to Provide Subject for International Symposium

Under the auspices of the Henry Ford Hospital, an international symposium on the reticular formation of the brain will be held in Detroit (March 14-16). A galaxy of researchers from here and abroad will present an impressive program on current concepts of the reticular formation in its neuroanatomic, physiologic, and psychologic aspects, as well as a special session on the development of ideas relating the mind with the brain (H. W. Magoun) .... Coming to the symposium from abroad are: Ross W. Adey (Victoria, Australia); A. Arduini (Pisa); Philip B. Bradley (Birmingham); Paul Dell (Paris); Henri Gastaut (Marseille); Geoffrey W. Harris (London); David H. Ingvar (Stockholm); R. Jung (Freiburg); and Sir Goeffrey Jefferson (Manchester).... AAN members on the program include H. W. Magoun (chairman), J. D. French, R. N. DeJong, and A. A. Ward, Jr. of the advisory program committee; Lorne D. Proctor (co-chairman), W. C. Noshay, and R. T. Costello of the local program committee; as well as H. H. Jasper, W. J. H. Nauta, Arnold B. and Madge Sheibel, V. E. Amassian, Mary A. B. Brazier, R. B. Livingston, J. L. O'Leary, E. F. Domino, D. P. Purpura, D. B. Lindsley, Frank Morrell, and J. D. Lilly.

Conference on Aging in the Nervous System

About 50 scientists convened at the National Institute of Neurological Diseases and Blindness in Bethesda (Jan. 30-Feb. 1) to discuss new research leads and approaches to the problem of aging in the nervous system. With E. V. Cowdry of Washington University (St. Louis) serving as honorary chairman, the sessions were conducted by the co-chairmen, James E. Birren and William F. Windle. Matters under discussion comprised structural changes in the nervous system, regeneration, cellular physiology, histochemistry, biochemistry, metabolism, and circulation of the brain, as well as neurologic and psychologic functions as related to the aging process. In addition to the

chairmen, the list of conferees included Edward Dempsey, Louis B. Flexner, Harold E. Himwich, Albert I. Lansing, Louis Sokoloff, Lewis D. Stevenson, Eugene Streicher, Harry H. Wilcox, and Abner Wolf.

Houston Neurological Society to Discuss Encephalitis

In its fifth annual scientific session, the Houston Neurological Society will conduct a symposium on "Virus Encephalitis" at the Texas Medical Center (March 1). Jordi Casals of the Rockefeller Foundation Virus Laboratories will introduce the comprehensive program which will concentrate on many aspects of virus encephalitis: epidemiology (E. H. Lennette), clinical and laboratory diagnosis (Frederick C. Robbins), sequelae (Knox H. Finley), neuropathology (Webb Haymaker), and trends in control (Herald R. Cox). E. C. Alvord leads the program committee, and the sessions are to be moderated by Russell J. Blattner, professor of pediatrics at Baylor University College of Medicine.... Inquiries should be directed to Dr. Claude Pollard, Jr., Secretary of the Houston Neurological Society, 411 Hermann Professional Bldg., Houston 25, Texas.

* * * * * *

Epilepsy Colloquium to be Held at Bethesda

Under the auspices of the Advisory Council of the National Institute of Neurological Diseases and Blindness, the Second International Colloquium on Temporal Lobe Epilepsy will be held at Bethesda, Maryland (March 21-23). Wilder Penfield and William G. Lennox will preside as honorary presidents and Henri Gastaut (Marseille) and A. Earl Walker as co-presidents. This meeting is a sequel to the First International Colloquium on Temporal Lobe Epilepsy organized by G. Morin, dean, and H. Gastaut, professor of neurophysiology at the University of Marseille (November 1954).... Beginning with a summary of the First International Colloquium by Gastaut, the program will proceed to a consideration of new concepts in electroencephalography and neurophysiology of the temporal lobe. J. Droogleever-Fortuyn (Groningen, Holland) will moderate these sessions, which include contributions from H. H. Jasper, J. D. Green, Maitland Baldwin, C. Ajmone-Marsan, and F. A. Gibbs. Also, in these sessions will be a presentation on clinical-electrographic correlations of temporal lobe seizures by H. Gastaut and M. Vigouroux. Next on the program (March 22) will be a presentation of new concepts of the pathologic aspects, to be moderated by P. Yakovlev and to include presentations by N. Malamud, W. Scholz (Munich), R. M. Norman (Bristol, England), C. B. Courville, as well as the collaborative studies of A. Meyer (London) and H. Gastaut; L. van Bogaert and H. Gastaut; R. Toga, R. Naquet, and H. Gastaut.... The official dinner will be held that evening,

followed with presentations by H. W. Magoun and D. B. Tower, who will discuss the biochemical lesion in seizures.... A highlight of the colloquium (morning of March 23) will be the presentation of several surgical series on temporal ablations, giving the clinical, electroencephalographic, and anatomic findings by Theodore Rasmussen and H. H. Jasper, Percival Bailey and F. A. Gibbs, J. E. Paillas (Marseille), Maitland Baldwin and C. Ajmone-Marsan, M. A. Falconer (London) and collaborators, and A. E. Walker. The discussions are to be opened by Paulo Niemeyer (Rio de Janeiro).... On the afternoon of March 23, the clinical aftermaths of temporal lobectomy will be presented by Heinrich Kluver, Hrayr Terzian (Italy), Percival Bailey, and Marianne L. Simmel. The discussion will be opened by H. Houston Merritt.... A summary of the proceedings and conclusions of the colloquium will be abstracted and duplicated for the use of members of the First International Congress of Neurological Sciences who will attend the Ve Reunion of the International League Against Epilepsy in Brussels, July 21.

Briefs A Conference on the History and Philosophy of Knowledge Concerning Brain Function has been tentatively planned to be held in London in July, prior to the meeting of the First International Congress of Neurological Sciences.... The new officers of the American Board of Psychiatry and Neurology are George N. Raines, president; Paul I. Yakovlev, vice-president; David A. Boyd, Jr. remains as secretary-treasurer. L. McKendree Eaton was elected as the new member from the AMA section. Francis M. Forster and William Malamud were reappointed for a period of four years.... Dr. R. M. Norman, in charge of the Neuropathological Laboratory, Frenchay Hospital, Bristol, England, has come to NINDB as a visiting scientist for a period of six months, on the collaborative project in cerebral palsy....

Percy Bailey

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"Recent studies have shown the importance of psychogenic factors and personality disorders in allergic diseases," Dr. Eisenberg explained. "Tranquilizing drugs can serve a useful purpose in allergic individuals to relieve certain psychiatric states which tend to aggravate the physical manifestations of their disease. While no case was cured in this study, many patients were made more comfortable, appeared to tolerate their symptoms much better, and showed a lessening of signs, such as wheezing, skin eruptions, etc."

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For Pulmonary Conditions
TRANSPULMIN®
3% solution Quinine with 2½% Camphor for Intramuscular Injection.

REVIEW COURSES IN BASIC and CLINICAL NEUROLOGY

APRIL 22, 23, 24, 1957

Preceding the

1957 AMERICAN ACADEMY OF NEUROLOGY MEETING

Sheraton Plaza Hotel, Boston, Massachusetts

NEUROPATHOLOGY—April 22, 1957. Dr. Fae Y. Tichy. Fees: Juniors: $15.00; Fellows, Actives, and Associates: $20.00; Non-members: $30.00. Deposit on slide box: $25.00 (all membership categories).

NEUROROENTGENOLOGY—April 22, 1957. Dr. A. L. Sahs. Fees: Juniors: $10.00; Fellows, Actives, and Associates: $15.00; Non-members: $20.00.

PAIN: ITS MECHANISM AND MANAGEMENT—April 22, 1957. Dr. Charles A. Kane. Fees: Juniors: $10.00; Fellows, Actives, and Associates: $15.00; Non-members: $20.00.

EPISODIC DISORDERS OF THE NERVOUS SYSTEM—April 23, 1957. Dr. F. M. Forster. Fees: Juniors: $10.00; Fellows, Actives, and Associates: $15.00; Non-members: $20.00.

NEUROCHEMISTRY—April 23, 1957. Dr. D. B. Tower. Fees: Juniors: $10.00; Fellows, Actives, and Associates: $15.00; Non-members: $20.00.

THE BRAIN AND ITS COMMUNICATION SYSTEMS—April 23, 1957. Dr. G. H. Glaser. Fees: Juniors: $10.00; Fellows, Actives, and Associates: $15.00; Non-members: $20.00.

CURRENT ADVANCES IN NEUROLOGY—April 24, 1957. Dr. Joe R. Brown. Fees: Juniors: $10.00; Fellows, Actives, and Associates: $15.00; Non-members: $20.00.

NEUROPHARMACOLOGY—April 24, 1957. Dr. Maynard M. Cohen. Fees: Juniors: $10.00; Fellows, Actives, and Associates: $15.00; Non-members: $20.00.

ENROLLMENT FOR ALL COURSES IS LIMITED

Priority will be determined by date of application

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Outline of each course, application and further information may be obtained from

Mrs. J. C. McKinley, Executive Secretary

3501 East 54th St., Minneapolis 17, Minnesota

This is a normal myelogram in which ***Pantopaque Contrast Medium*** outlines the lower lumbar subarachnoid space and the sacral cul-de-sac. It is an anteroposterior radiograph made with the spot-film device after tilting the patient to the semierect position on the fluoroscopic table. This is to be compared with the myelogram at the right showing herniation of the fifth lumbar intervertebral disk.

The left lateral aspect of the ***Pantopaque*** column in the subarachnoid space is smoothly indented at the level of the fifth lumbar-first sacral intervertebral space. The left nerve root is not filled, while the right sheath is well visualized.

"PANTOPAQUE" *is the registered trademark under which all leading x-ray dealers supply the compound ethyl iodophenylundecylate, which is synthesized by the Research Laboratories of Eastman Kodak Company and prepared as the myelographic contrast medium Iodophenylate Injection, U.S.P., by Lafayette Pharmacal Company. The trademark serves to indicate to the radiologist continuity of experience in the manufacture of this medium.*